

100.0% PROCESSED 37182 ITERATIONS
SEARCH TIME: 00.00.01

594 ANSWERS

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(FILE 'HOME' ENTERED AT 07:01:07 ON 04 MAR 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003

L1 STR
L2 19 S L1
L3 594 S L1 FUL
SAV L3 KWON071/A

FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003

L4 40 S L3
E BUSER S/AU
L5 10 S E3,E6,E7
E FORD A/AU
L6 33 S E3,E16,E17
L7 37 S E63,E65
E FORD TONY/AU
E HOFFMANN T/AU
L8 135 S E3-E9
E HOFFMANN TOR/AU
L9 57 S E4
E LENZ B/AU
L10 29 S E3-E9
E SLEIGHT A/AU
L11 52 S E4,E6-E8
E VANKAN P/AU
L12 23 S E3-E5
E ROCHE/PA,CS
L13 21472 S E3,E4
L14 61 S E27-E46
E ROHAN/PA,CS
L15 2 S E3,E4
L16 10 S L4 AND L5-L15
E PROSTATE/CT
E E5+ALL
L17 2309 S E2
L18 1988 S E12
L19 22609 S E20-E19+NT
L20 1 S L4 AND L17-L19
L21 1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L22 1 S L20,L21
L23 1 S L22 AND L16
L24 969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
L25 5 S L24 AND L17-L19
L26 2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L27 6 S L25,L26
L28 1 S L23 AND L27
L29 5 S L27 NOT L28
SEL DN AN 1 4 5
L30 3 S E1-E7 AND L29
L31 4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
L32 4 S L28,L30,L31
L33 39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
L34 47 S GR205171 OR GR() (205171 OR 205 171)
L35 5 S HSP117 OR HSP 117
L36 36 S L703606 OR L() (703606 OR 703 606)

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L37      23 S L668169 OR L() (668169 OR 668 169)
L38      4 S LY303241 OR LY() (303241 OR 303 241)
L39      12 S LY306740 OR LY() (306740 OR 306 740)
L40      21 S MK869 OR MK 869
L41      6 S R544 OR R 544
L42      5 S SPANTIDE III
L43      11 S WIN62577 OR WIN() (62577 OR 62 577)
L44      5 S GR103537 OR GR() (103537 OR 103 537)
L45      13 S L758298 OR L() (758298 OR 758 298)
L46      9 S NKP608 OR NKP 608
L47      17 S CGP49823 OR CGP() (49823 OR 49 823)
L48      494 S CP96345 OR CP() (96345 OR 96 345)
L49      246 S CP99994 OR CP() (99994 OR 99 994)
L50      24 S CP122721 OR CP() (122721 OR 122 721)
L51      129 S FK888 OR FK 888
L52      119 S GR82334 OR GR() (82334 OR 82 334)
L53      41 S GR94800 OR GR() (94800 OR 94 800)
L54      20 S L733060 OR L() (733060 OR 733 060)
L55      16 S L742694 OR L() (742694 OR 742 694)
L56      10 S L754030 OR L() (754030 OR 754 030)
L57      30 S LY303870 OR LY() (303870 OR 303 870)
L58      9 S MEN11149 OR MEN() (11149 OR 11 149)
L59      10 S PD154075 OR PD() (154075 OR 154 075)
L60      250 S RP67580 OR RP() (67580 OR 67 580)
L61      18 S RPR100893 OR RPR() (100893 OR 100 893)
L62      1 S SPENDIDE
L63      32 S SENDIDE
L64      55 S SPANTIDE II
L65      217 S SR140333 OR SR() (140333 OR 140 333)
L66      0 S WIN41708 OR WIN() (41708 OR 41 708)
L67      11 S WIN62577 OR WIN() (62577 OR 62 577)
L68      410 S SR48968 OR SR() (48968 OR 48 968)
L69      69 S L659877 OR L() (659877 OR 659 877)
L70      74 S MEN10627 OR MEN() (10627 OR 10 627)
L71      14 S SR144190 OR SR() (144190 OR 144 190)
L72      41 S GR94800 OR GR() (94800 OR 94 800)
L73      149 S SR142801 OR SR() (142801 OR 142 801)
L74      159 S R820 OR R 820
L75      14 S R486 OR R 486
L76      13 S SB222200 OR SB() (222200 OR 222 200)
L77      13 S L758298 OR L() (758298 OR 758 298)
L78      0 S NK608 OR NK 608
L79      3 S MK608 OR MK 608
L80      2 S CGP47899 OR CGP() (47899 OR 47 899)
L81      16 S MEN11467 OR MEN() (11467 OR 11 467)
L82      18 S GR203040 OR GR() (203040 OR 203 040)
L83      13 S L732138 OR L() (732138 OR 732 138)
L84      1 S L4 AND L34-L83
L85      2 S WIN41908 OR WIN() (41908 OR 41 908)
L86      349 S SPANTIDE
L87      1 S L4 AND L85,L86
L88      1 S L84,L87
          SEL RN

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FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003

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L89      186 S E8-E193
L90      129 S L89 AND L3
L91      1 S 351383-26-1
L92      56 S L89 NOT L90,L91
L93      7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
L94      6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
L95      43 S L92 NOT L93,L94
L96      6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1

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FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003

L97 46 S L95,L96

FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003

L98 964 S L97
L99 3 S L4 AND L98
L100 3 S L88,L99
L101 3 S L100 AND L4-L16
L102 6 S L32,L101
E TACKYKININ RECEPTOR/CT
E TACHYKININ RECEPTOR/CT
L103 1581 S E5,E6
L104 223 S E14
E E4+ALL
L105 3707 S E10,E11,E9+NT
E E27+ALL
L106 2037 S E8,E7+NT
E E6+ALL
L107 3401 S E7,E8,E6+NT
E E20
L108 2087 S E3-E21
L109 638 S E22-E25
L110 13 S L4 AND L103-L109
L111 3 S L102 AND L110
L112 6 S L102,L111
L113 6 S L112 AND L4-L88
L114 3 S L113 AND L17-L19
L115 2 S L113 AND (BHP OR BENIGN(L) PROSTAT?(L) HYPER?)
L116 4 S L114,L115
L117 12 S L110,L113 NOT L116
L118 12 S L117 AND L4-L88,L98-L109

FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:04:40 ON 04 MAR 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 4 Mar 2003 VOL 138 ISS 10

FILE LAST UPDATED: 3 Mar 2003 (20030303/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l116 all tot

L116 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2003 ACS

AN 2003:151546 HCAPLUS

TI New approaches in the treatment of overactive bladder: Targeting
adrenergic **receptors** and **neurokinin receptors**

AU Ishizuka, O.

CS Department of Urology, Shinshu University School of Medicine, Matsumoto,
390-8621, Japan

SO Current Medicinal Chemistry: Central Nervous System Agents (2003), 3(1),
43-47
CODEN: CMCCCO; ISSN: 1568-0150

PB Bentham Science Publishers Ltd.

DT Journal

LA English

CC 1 (Pharmacology)

AB Bladder outlet obstruction, such as **benign prostatic hypertrophy**, and neurogenic bladder with cerebro-vascular disease and Parkinson's disease, not only cause difficulty in urination, but also overactive bladder. This overactive condition is currently a major health concern, in terms of quality of life. Bladder outlet obstruction leads to bladder **hypertrophy**, and changes in the nervous control of micturition. **Hypertrophied** detrusor muscles release nerve growth factor, which also leads to changes in nervous control of micturition, esp. sympathetic nerve and c-fiber mediated control. Adrenergic **receptors** comprise certain subtypes, .alpha.1A, .alpha.1B, .alpha.1D, .alpha.2A, .alpha.2B, .alpha.2D, .beta.1, .beta.2, .beta.3. Recently, .alpha.1D and .beta.3 **receptors** are of particular interest with regard to their functional role in overactive bladder. **Tachykinins** are the main neuropeptides of c-fiber mediated nervous control. Normally, this c-fiber is silent; however, in pathol. conditions, such as bladder outlet obstruction and neurogenic bladder, it becomes activated and causes overactive bladder. Recently, **antagonists of tachykinin receptors**, **neurokinin** (NK) 1, 2, 3, have become of interest in regard to their role in the treatment of overactive bladder. This review describes some of the changes in adrenergic and **NK receptors** in the central nervous system and the spinal micturition center in the overactive bladder, and a new approach to treatment that targets these **receptors**.

L116 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:832668 HCAPLUS

DN 137:337901

TI Preparation and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**

IN Buser, Susanne; Ford, Anthony P. D. W.; Hoffmann, Torsten; Lenz, Barbara; Sleight, Andrew John; Vankan, Pierre

PA F. Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61P013-08

ICS A61K031-44; A61K031-455

CC 28-14 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 27

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002085458	A2	20021031	WO 2002-EP1085	20020202 <--
	W:				
					AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
					CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
					GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
					LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,

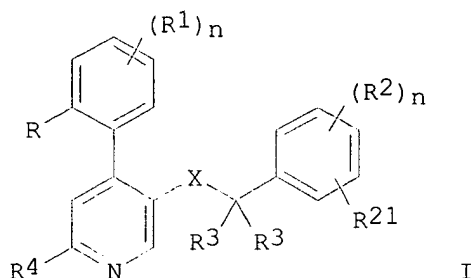
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
 UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003004157 A1 20030102 US 2002-71570 20020208 <--

PRAI EP 2001-109853 A 20010423 <--

OS MARPAT 137:337901

GI



AB Use of an NK-1 receptor antagonist

for the treatment or prevention of **benign prostatic hyperplasia (BPH)** is claimed. The preferred **NK-1 receptor antagonists** are compds. of the

general formula [I; R = H, alkyl, alkoxy, halo, CF₃; R₁ = H, halo; RR₁ = CH:CHCH:CH; R₂, R₂₁ = H, halo, CF₃, alkyl, alkoxy, cyano; R₂R₂₁ = CH:CHCH:CH, optionally substituted by 1-2 alkyl, halo, alkoxy; R₃ = H, alkyl; R₃R₃C = cycloalkyl; R₄ = H, N(R₅)₂, NR₅(CH₂)_nOH, cyclic tertiary amine, etc.; X = CONR₅, (CH₂)_pO, NR₅(CH₂)_p, etc.; R₅ = H, cycloalkyl, Ph, PhCH₂, alkyl; n = 0-4; p = 1-3]. Preferred compds. are 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)isobutyramide, 3-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]isobutyramide, 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1.λ.6-thiomorpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methylisobutyramide, and 2-(3,5-bis-trifluoromethylphenyl)-N-[6-(1,1-dioxo-1.λ.6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methylisobutyramide. Thus, 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-(6-thiomorpholin-4-yl-4-o-tolylpyridin-3-yl)isobutyramide (prepn. given) oxone were stirred 2 days at room temp. to give 2-(3,5-bis-trifluoromethylphenyl)-N-[6-(1,1-dioxo-1.λ.6-thiomorpholin-4-yl)-4-o-tolylpyridin-3-yl]-N-methylisobutyramide. 2-(3,5-Bistrifluoromethylphenyl)-N-methyl-N-methyl-N-(6-morpholin-4-yl-4-o-tolylpyridin-3-yl)isobutyramide at 60 mg/kg/day orally in dogs reduced **prostate** wt. by 58% after 39 wk.

ST amide prepn benign prostatic hypertrophy

treatment; **nk1 receptor antagonist** amide prepn;

benign prostatic hypertrophy treatment
 pyridylamide

IT Tachykinin receptors

(**NK1 antagonists**; prepn. and use of amides as

NK-1 receptor antagonists against

benign prostatic hyperplasia)

IT Prostate gland

(**benign hyperplasia**, treatment; prepn. and use of

amides as **NK-1 receptor**

antagonists against **benign prostatic**

hyperplasia)

IT Human

(prepn. and use of amides as **NK-1 receptor**

antagonists against benign prostatic
hyperplasia)

IT 474026-03-4P 474026-04-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

(prepn. and use of amides as NK-1 receptor
antagonists against benign prostatic
hyperplasia)

IT 66619-84-9, WIN-41908 91224-37-2,
Spantide 125989-12-0, L-659877
126088-92-4, R 544 129176-97-2,
Spantide II 129623-01-4, GR
82334 132041-95-3, R486 132746-60-2,
CP-96345 135911-02-3, RP-
67580 136982-36-0, CP-99994
137012-28-3, L 668169 138449-07-7,
FK 888 141636-65-9, GR 94800
142001-63-6, SR-48968 144177-32-2,
WIN-62577 144425-84-3, L
703606 145742-28-5, CP-122721
148451-96-1, L 732138 148700-85-0,
L 733060 150705-88-7, CGP49823
153438-49-4, RPR 100893 154427-06-2,
Spantide III 155418-05-6, SR
140333 157351-81-0, MEN 10627
158991-23-2, PD 154075 159706-39-5,
L 742694 168266-90-8, GR205171
168398-02-5, GR203040 170566-51-5, LY
303241 170566-84-4, LY 303870
170567-08-5, LY 306740 170729-80-3,
MK-869 172673-20-0, L 758298
173050-51-6, SR-142801 173481-41-9,
CGP 47899 174635-69-9, SB222200
177707-12-9, NKP608 183673-27-0, HSP
-117 201152-86-5, SR 144190
206052-25-7, MEN 11149 214487-46-4,
MEN 11467 240436-53-7, MK
608 290296-41-2 290296-42-3
290296-43-4 290296-44-5 290296-45-6
290296-46-7 290296-47-8 290296-49-0
290296-50-3 290296-51-4 290296-59-2
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290296-71-8 290296-72-9 290296-73-0
290296-74-1 290296-75-2 290296-86-5
290296-87-6 290296-88-7 290296-89-8
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290296-96-7 290296-98-9 290296-99-0
290297-00-6 290297-01-7 290297-06-2
290297-18-6 290297-26-6 290297-30-2
290297-57-3 290297-58-4 290297-59-5
290297-61-9 290297-62-0 290297-65-3
290298-21-4 351383-26-1, GR 103537
391674-73-0 391674-74-1 391674-75-2
391674-76-3 391674-77-4 391674-79-6
391674-80-9 391674-81-0 391674-82-1
391674-83-2 391674-84-3 391674-85-4
391674-86-5 391674-87-6 391674-89-8
391674-90-1 391674-91-2 391674-92-3
391674-93-4 391674-94-5 391674-95-6
391674-97-8 391674-98-9 391674-99-0
391675-00-6 391675-01-7 391675-02-8

E 45

E 185-187

E 163

E 91

393508-70-8 393508-71-9 393508-72-0
 393508-73-1 393508-74-2 393508-75-3
 393508-76-4 393508-77-5 393508-78-6
 393508-79-7 393508-80-0 393508-81-1
 393508-82-2 393508-84-4 393508-91-3
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 401891-35-8 401891-36-9 401891-37-0
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 401891-41-6 401891-42-7 401891-43-8
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 401891-94-9 401892-00-0 401892-10-2
 401892-12-4 401892-24-8 401892-25-9
 401892-29-3 401892-38-4 401892-63-5
 474026-05-6 474026-06-7 474026-07-8
 474026-08-9 474026-09-0 474026-10-3
 474026-11-4 474026-12-5 474026-13-6
 474026-14-7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(prepn. and use of amides as **NK-1 receptor**
antagonists against **benign prostatic**
hyperplasia)

IT 123-90-0, Thiomorpholine 3282-30-2, Pivaloyl chloride 4548-45-2,
 2-Chloro-5-nitropyridine 16419-60-6, o-Tolylboronic acid 139911-29-8,
 4-Fluoro-2-methylphenylboronic acid 289686-69-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. and use of amides as **NK-1 receptor**
antagonists against **benign prostatic**
hyperplasia)

IT 219140-38-2P 471938-15-5P 474026-15-8P 474026-16-9P 474026-17-0P
 474026-18-1P 474026-20-5P **474026-21-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(prepn. and use of amides as **NK-1 receptor**
antagonists against **benign prostatic**
hyperplasia)

L116 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:753071 HCAPLUS

DN 131:346564

TI Method using a **tachykinin** antagonist for treating or preventing
 chronic nonbacterial prostatitis and prostatodynia

IN Guess, Harry A.; Pearson, Jay Dee; Waldstreicher, Joanne

PA Merck & Co., Inc., USA

SO PCT Int. Appl., 70 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-40

ICS A61K031-535

CC 1-12 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9959583	A1	19991125	WO 1999-US10736	19990514
	W:	AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,			

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9939938	A1	19991206	AU 1999-39938	19990514
US 6054455	A	20000425	US 1999-313002	19990517

PRAI US 1998-85866P P 19980518
 WO 1999-US10736 W 19990514

AB A **tachykinin receptor antagonist**, in particular a **neurokinin-1 receptor antagonist**, is useful for the treatment or prevention of chronic nonbacterial prostatitis and/or prostaticodynia.

ST **tachykinin receptor antagonist** nonbacterial prostatitis prostaticodynia; **neurokinin 1 receptor antagonist** prostatitis prostaticodynia

IT **Tachykinin receptors**
 (NK1 antagonists; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Antibiotics
 (carbapenem; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Prostate-specific antigen
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (conjugates; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT **Prostate gland**
 (disease, prostaticodynia; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Anti-inflammatory agents
 (nonsteroidal; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT **Prostate gland**
 (prostatitis; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Cholinergic antagonists
 (**tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT **Tachykinin receptors**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (**tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Analgesics
 (topical urinary; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Adrenoceptor antagonists
 (.alpha.1-, .alpha.1a; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT Adrenoceptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (.alpha.1A, blockers; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT 39391-18-9
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (2, inhibitors; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostaticodynia)

IT 83200-96-8D, Carbapenem, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotics; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT 9081-34-9, 5.alpha.-Reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bush; US 4822610 A 1989 HCAPLUS
(2) Gideon; US 5736144 A 1998
(3) Gormley; US 5629318 A 1997 HCAPLUS
(4) Oden; US 5580857 A 1996 HCAPLUS

L116 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:293223 HCAPLUS
DN 124:333868
TI Pharmacological characterization of **tachykinin** NK2 **receptors** on isolated human urinary bladder, prostatic urethra and prostate
AU Palea, Stefano; Corsi, Mauro; Artibani, Walter; Ostardo, Edoardo; Pietra, Claudio
CS Dep. Pharmacol., Glaxo Res. Lab., Verona, Italy
SO Journal of Pharmacology and Experimental Therapeutics (1996), 277(2), 700-705
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The contractile effects of two highly potent, selective and peptidase-resistant **neurokinin** (NK) 1 and NK2 **receptor** agonists, namely GR 73632 and GR 64349, resp., were investigated on smooth muscle strips dissected from specimens of human detrusor, prostatic urethra and prostate. Furthermore, the potencies of two peptidic NK2 **receptor** **antagonists**, GR 87389 and L 659837, in **antagonizing** GR 64349-induced contractions were compared in these three tissues. In human detrusor muscle the rank order of agonist potency was: [.beta.-Ala8-NKA-(4-10)] > GR 64349 >> NKA-(4-10) >> substance P (SP) = GR 73632 >> SP Me ester. The NK2 **receptor** **antagonist**, GR 87389, **antagonized** GR 64349-induced contractions in a competitive manner, whereas L 659837 was a noncompetitive **antagonist**. In the prostatic urethra the rank order of agonist potency was GR 64349 > NKA-(4-10) > SP > GR 73632, whereas in the prostate it was: GR 64349 >> [.beta.-Ala8-NKA-(4-10)] > NKA-(4-10) > SP; GR 73632 was ineffective up to 30 .mu.M. In the prostatic urethra and in the prostate GR 87389 was a noncompetitive **antagonist** with a potency similar to that exhibited in the detrusor. On the contrary, L 659837 appeared to be a competitive **antagonist** in the prostate and in the prostatic urethra, having approx. the similar potency in these two tissues. The selective NK3 agonist senktide was ineffective up to 30 .mu.M in all three tissues. These results are discussed in the view of the proposed NK2 **receptor** subtypes and considering possible therapeutic implications in the treatment of urinary bladder disorders.

ST **tachykinin** NK2 **receptor** bladder urethra prostate
IT Bladder
Prostate gland

Urethra

(**tachykinin NK2 receptor** pharmacol.
characterization in isolated human urinary bladder and prostatic
urethra and prostate)

IT **Kinin receptors**
Receptors

RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological
study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC
(Process)

(**tachykinin NK2, tachykinin NK2 receptor**
pharmacol. characterization in isolated human urinary bladder and
prostatic urethra and prostate)

IT 33507-63-0, Substance P (peptide) 76260-78-1, Substance P methyl ester
97559-35-8, **Neurokinin A**-(4-10) 122063-01-8, .beta.-Ala8-
neurokinin A(4-10) 133156-06-6, GR 73632 137593-52-3, GR 64349

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)

(**tachykinin NK2 receptor** pharmacol.
characterization in isolated human urinary bladder and prostatic
urethra and prostate)

=> d 1118 all fhitr tot

L118 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 2003:57902 HCAPLUS

DN 138:117662

TI Use of **NK-1 receptor antagonists**
for the treatment of brain, spinal or nerve injury

IN **Hoffmann, Torsten**; Nimmo, Alan John; **Sleight, Andrew**;
Vankan, Pierre; Vink, Robert

PA F. Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 36 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-435

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006016	A2	20030123	WO 2002-EP7323	20020703
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRAI EP 2001-116812 A 20010710

OS MARPAT 138:117662

AB The invention discloses the use of an **NK-1**
receptor antagonist (Markush included), e.g.
N-(3,5-bis-trifluoromethylbenzyl)-N-methyl-6-(4-methylpiperazin-1-yl)-4-o-
tolylnicotinamide, optionally in combination with a magnesium salt, for
the treatment and/or prevention of brain, spinal or nerve injury. The
invention also relates to pharmaceutical compns. comprising one or more
such **NK-1 receptor antagonists**, optionally in
combination with a magnesium salt, and a pharmaceutically acceptable

excipient, for the treatment and/or prevention of brain, spinal or nerve injury.

ST NK1 receptor antagonist brain spinal nerve injury; nicotinamide deriv NK1 antagonist brain spinal nerve injury

IT Drug delivery systems
(NK-1 receptor antagonist for treatment of brain, spinal or nerve injury)

IT Cognition enhancers
(NK-1 receptor antagonist for treatment of brain, spinal or nerve injury, and use with magnesium)

IT **Tachykinin receptors**
(NK1 antagonists; NK-1 receptor antagonist for treatment of brain, spinal or nerve injury)

IT Mental disorder
(cognitive, cognitive function loss after brain injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Cognition
(disorder, cognitive function loss after brain injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
(edema; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
Nerve, disease
Spinal cord
(injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

IT Behavior
(motor; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Cytoprotective agents
(neuroprotectants; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Biological transport
(permeation, blood-brain barrier post-traumatic permeability; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Blood-brain barrier
(post-traumatic permeability; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Drug delivery systems
(solns., injection; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
(trauma; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT 290296-41-2 290296-42-3 290296-43-4
290296-44-5 290296-45-6 290296-46-7
290296-47-8 290296-49-0 290296-50-3
290296-51-4 290296-59-2 290296-66-1
290296-67-2 290296-68-3 290296-72-9
290296-73-0 290296-74-1 290296-75-2
290296-84-3 290296-85-4 290296-86-5
290296-87-6 290296-88-7 290296-89-8
290296-90-1 290296-91-2 290296-92-3
290296-93-4 290296-94-5 290296-95-6
290296-96-7 290296-98-9 290296-99-0

290297-00-6 290297-01-7 290297-05-1
 290297-18-6 290297-26-6 290297-30-2
 290297-57-3 290297-58-4 290297-59-5
 290297-61-9 290297-62-0 290297-63-1
 290297-64-2 290297-65-3 290297-66-4
 290298-21-4 391674-73-0 391674-74-1
 391674-75-2 391674-76-3 391674-77-4
 391674-78-5 391674-79-6 391674-80-9
 391674-81-0 391674-82-1 391674-83-2
 391674-84-3 391674-85-4 391674-86-5
 391674-87-6 391674-89-8 391674-90-1
 391674-91-2 391674-92-3 391674-93-4
 391674-94-5 391674-95-6 391674-97-8
 391674-98-9 391674-99-0 391675-00-6
 391675-01-7 391675-02-8 393508-70-8
 393508-71-9 393508-72-0 393508-73-1
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 393508-80-0 393508-81-1 393508-82-2
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 401891-33-6 401891-34-7 401891-35-8
 401891-36-9 401891-37-0 401891-38-1
 401891-39-2 401891-40-5 401891-42-7
 401891-43-8 401891-44-9 401891-45-0
 401891-55-2 401891-63-2 401891-67-6
 401891-70-1 401891-87-0 401891-90-5
 401891-91-6 401891-94-9 401892-00-0
 401892-10-2 401892-12-4 401892-24-8
 401892-25-9 401892-29-3 401892-38-4
 401892-63-5 474026-07-8 474026-11-4
 474026-12-5 474026-13-6 488780-92-3
 488780-93-4

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(NK-1 receptor antagonist for
 treatment of brain, spinal or nerve injury)

IT 7439-95-4, Magnesium, biological studies

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(NK-1 receptor antagonist for
 treatment of brain, spinal or nerve injury, and use with magnesium)

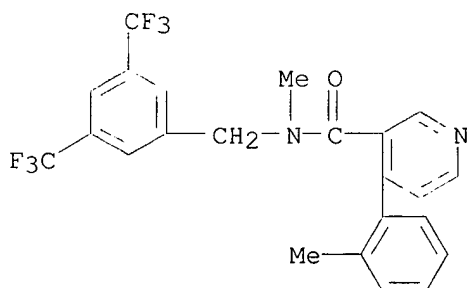
IT 290296-41-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(NK-1 receptor antagonist for
 treatment of brain, spinal or nerve injury)

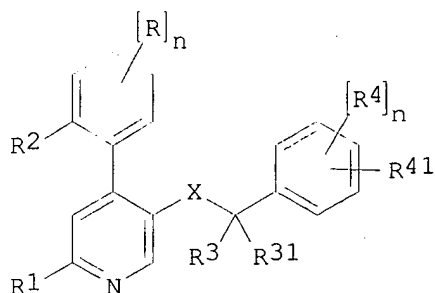
RN 290296-41-2 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-N-methyl-
 4-(2-methylphenyl)- (9CI) (CA INDEX NAME)



L118 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2003 ACS
 AN 2002:157739 HCAPLUS
 DN 136:216651
 TI Preparation of 4-phenylpyridines as **neurokinin-1 receptor antagonists**
 IN Godel, Thierry; Hoffmann, Torsten; Schnider, Patrick; Stadler, Heinz
 PA F. Hoffmann-La Roche A.-G., Switz.
 SO PCT Int. Appl., 108 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C07D213-74
 ICS C07D213-82; C07D213-79; C07D213-75; C07D413-04; C07D401-04;
 C07D409-04; C07D401-06; C07D401-12; C07D417-04; A61P025-00;
 A61P029-02; A61K031-4427; A61K031-455
 CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
 Section cross-reference(s): 1, 63
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002016324	A1	20020228	WO 2001-EP8686	20010727 <--
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002012118	A5	20020304	AU 2002-12118	20010727 <--
	US 2002040040	A1	20020404	US 2001-922066	20010803 <--
PRAI	EP 2000-117003	A	20000808 <--		
	WO 2001-EP8686	W	20010727		
OS	MARPAT 136:216651				
GI					



I

AB The title compds. [I; R = H, halo; R1 = (C.tplbond.C)mR11, (CR'=CR'')mR11 (wherein R11 = halo, CN, aryl, etc.; R', R'' = H, OH, alkyl, etc.); R2 = H, alkyl, alkoxy, halo, CF3; R3, R31 = H, alkyl or form together with the C atom to which they are attached a cycloalkyl group; R4, R41 = H, halo, CF3, alkyl, alkoxy; R and R2 or R4 and R41 may be together CH=CHCH=CH, optionally substituted by one or two substituents selected from alkyl, halo or alkoxy; X = CONR8, (CH2)pO, (CH2)pNR8, NR8CO, NR8(CH2)p (wherein

R8 = H, alkyl); n = 1-2; m = 0-4; p = 1-2] which are **antagonists** of the **Neurokinin 1 (NK-1, substance P) receptor**, and therefore useful in the treatment of diseases, related to this **receptor**, were prepd. and formulated. E.g., a multi-step synthesis of I [R = H; R1 = N(OH)CH₂CH₂OH; R2 = Me; R3, R31 = Me; R4 = 3-CF₃; R41 = 5-CF₃; X = NMeCO] which showed pK_i of 9.29 in human NK1 **receptor** assay, was given.

ST phenylpyridine prepn formulation neurokinin NK1 antagonist; tachykinin NK1 antagonist phenylpyridine prepn formulation

IT **Tachykinin receptors**

(NK1 antagonists; prepn. of 4-phenylpyridines as neurokinin-1 receptor antagonists)

IT Human

(prepn. of 4-phenylpyridines as neurokinin-1 receptor antagonists)

IT 393508-84-4P 401891-34-7P 401891-36-9P

401891-37-0P 401891-41-6P 401891-47-2P

401891-48-3P 401891-49-4P 401891-53-0P

401891-54-1P 401891-55-2P 401891-56-3P

401891-58-5P 401891-59-6P 401891-60-9P

401891-63-2P 401891-66-5P 401891-67-6P

401891-69-8P 401891-78-9P 401891-80-3P

401891-81-4P 401891-86-9P 401891-88-1P

401891-91-6P 401891-97-2P 401891-98-3P

401892-01-1P 401892-02-2P 401892-09-9P

401892-12-4P 401892-18-0P 401892-23-7P

401892-28-2P 401892-36-2P 401892-40-8P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of 4-phenylpyridines as neurokinin-1 receptor antagonists)

IT 393508-91-3P 401891-32-5P 401891-33-6P

401891-35-8P 401891-38-1P 401891-39-2P

401891-40-5P 401891-42-7P 401891-43-8P

401891-44-9P 401891-45-0P 401891-46-1P

401891-50-7P 401891-51-8P 401891-52-9P

401891-57-4P 401891-61-0P 401891-62-1P

401891-64-3P 401891-65-4P 401891-68-7P

401891-70-1P 401891-71-2P 401891-72-3P

401891-73-4P 401891-74-5P 401891-75-6P

401891-76-7P 401891-77-8P 401891-79-0P

401891-82-5P 401891-83-6P 401891-84-7P 401891-85-8P

401891-87-0P 401891-89-2P 401891-90-5P

401891-92-7P 401891-93-8P 401891-94-9P

401891-95-0P 401891-96-1P 401891-99-4P

401892-00-0P 401892-03-3P 401892-04-4P

401892-05-5P 401892-06-6P 401892-07-7P

401892-08-8P 401892-10-2P 401892-11-3P

401892-13-5P 401892-14-6P 401892-15-7P

401892-16-8P 401892-17-9P 401892-19-1P

401892-20-4P 401892-21-5P 401892-22-6P

401892-24-8P 401892-25-9P 401892-26-0P

401892-27-1P 401892-29-3P 401892-30-6P

401892-31-7P 401892-32-8P 401892-33-9P

401892-34-0P 401892-35-1P 401892-37-3P

401892-38-4P 401892-39-5P 401892-41-9P

401892-42-0P 401892-43-1P 401892-44-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 4-phenylpyridines as neurokinin-1

receptor antagonists)

IT 60-56-0, 2-Mercapto-1-methylimidazole 66-25-1, Hexanal 75-65-0, tert-Butanol, reactions 98-17-9, 3-Hydroxybenzotrifluoride 100-39-0, Benzyl bromide 100-52-7, Benzaldehyde, reactions 108-03-2, 1-Nitropropane 109-75-1, Allylcyanide 110-91-8, Morpholine, reactions 140-67-0, 4-Allylanisole 541-41-3, Ethyl chloroformate 543-20-4, Succinyl chloride 591-50-4, Iodobenzene 627-32-7, 3-Iodopropanol 637-96-7, Sarcosine hydrochloride 693-98-1, 2-Methylimidazole 696-63-9, 4-Methoxythiophenol 762-62-9, 4,4-Dimethyl-1-pentene 765-30-0, Cyclopropylamine 767-00-0, 4-Hydroxybenzonitrile 872-85-5, 4-Pyridinecarboxaldehyde 873-55-2, Sodium benzenesulfinate 873-62-1, 3-Hydroxybenzonitrile 1066-54-2, Trimethylsilylacetylene 1692-15-5, 4-Pyridylboronic acid 1692-25-7, 3-Pyridylboronic acid 1765-93-1, 4-Fluorophenylboronic acid 2365-48-2, Methyl thioglycolate 2637-34-5, 2-Mercaptopyridine 2935-90-2, Methyl 3-mercaptopropionate 3282-30-2, Pivaloyl chloride 3678-63-5, 4-Chloro-2-methylpyridine 3900-89-8, 2-Chlorophenylboronic acid 4023-34-1, Cyclopropanecarboxylic acid chloride 4548-45-2, 2-Chloro-5-nitropyridine 4916-55-6, 3-(Bromomethyl)pyridine hydrobromide 5326-23-8, 6-Chloronicotinic acid 5720-06-9, 2-Methoxyphenylboronic acid 5720-07-0, 4-Methoxyphenylboronic acid 7051-34-5, (Bromomethyl)cyclopropane 7223-50-9, N-Propargylphthalimide 10365-98-7, 3-Methoxyphenylboronic acid 13472-85-0, 5-Bromo-2-methoxypyridine 13831-31-7, Acetoxyacetyl chloride 14763-60-1, 4-Methylsulfonylphenol 15570-12-4, 3-Methoxythiophenol 16114-47-9 16419-60-6, o-Tolylboronic acid 24854-43-1, 3-Mercapto-4-methyl-4H-1,2,4-triazole 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium chloride 57260-71-6, 1-tert-Butoxycarbonylpiperazine 68337-15-5, 4-(1,2,4-Triazol-1-yl)phenol 73870-24-3, 4-(Bromomethyl)pyridine hydrobromide 75233-61-3, 2-(2-Nitroethoxy)tetrahydropyran 76782-82-6 97674-02-7, 1-Ethoxyvinyltributyltin 99768-12-4, 4-Methoxycarbonylphenylboronic acid 126747-14-6, 4-Cyanophenylboronic acid 139911-29-8, (4-Fluoro-2-methylphenyl)boronic acid 159820-24-3 168267-41-2, 3,4-Difluorophenylboronic acid 206551-43-1 286961-14-6 289686-69-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of 4-phenylpyridines as **neurokinin-1**

receptor antagonists)

IT 22282-65-1P 26820-62-2P 52023-68-4P 53939-30-3P, 5-Bromo-2-chloropyridine 54189-82-1P, 6-Chloro-N-methylnicotinamide 290296-68-3P 290296-83-2P 290296-89-8P 290296-93-4P 290297-13-1P 290297-14-2P 290297-32-4P 290297-33-5P 290297-34-6P 290297-35-7P 290297-36-8P 290297-39-1P 290297-40-4P 290297-41-5P 290297-53-9P 290298-22-5P 342416-98-2P 391674-73-0P 391674-74-1P 393508-76-4P 401892-45-3P 401892-46-4P 401892-47-5P 401892-48-6P 401892-49-7P 401892-50-0P 401892-51-1P 401892-52-2P 401892-53-3P 401892-54-4P 401892-55-5P 401892-56-6P 401892-57-7P 401892-58-8P 401892-59-9P 401892-60-2P 401892-61-3P 401892-62-4P 401892-63-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 4-phenylpyridines as **neurokinin-1**

receptor antagonists)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

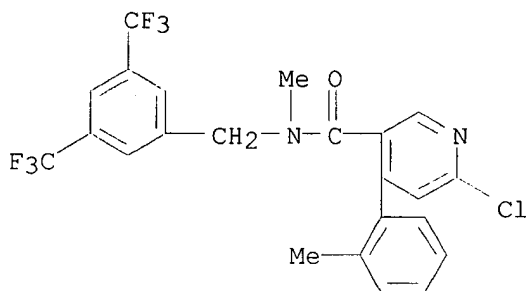
- (1) Grugn; WO 9719926 A 1997 HCAPLUS
- (2) Hoffmann La Roche; WO 0050398 A 2000 HCAPLUS
- (3) Hoffmann La Roche; EP 1035115 A 2000 HCAPLUS
- (4) Hoffmann La Roche; EP 1103545 A 2001 HCAPLUS
- (5) Ikeura, Y; CHEMICAL AND PHARMACEUTICAL BULLETIN 1997, V45(10), P1642 HCAPLUS

IT 393508-84-4P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

RN 393508-84-4 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-6-chloro-N-methyl-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)



L118 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:90050 HCAPLUS

DN 136:134681

TI Preparation of 4-phenylpyridine derivatives as **neurokinin-1 receptor antagonists**

IN Hoffmann, Torsten; Schnider, Patrick; Stadler, Heinz

PA F. Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D521-00

ICS C07D213-82; C07D401-04; C07D213-75; C07D413-04; A61K031-4427;
 A61K031-465; A61P025-00; A61P029-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008232	A1	20020131	WO 2001-EP8432	20010720 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002038030	A1	20020328	US 2001-901311	20010709 <--
PRAI EP 2000-115846	A	20000724 <--		
OS MARPAT 136:134681				
GI				

AB The title compds. [I or II; R1 = III, 2,3-dihydro-[1,4]oxazin-4-yl, imidazol-1-yl, [1,2,4]triazol-1-yl, NH(CH₂)₂OH, NR₃COCH₃, NR₃Cocyclopropyl; R₂ = Me, Cl; R₃ = H, Me; R = H, (CH₂)₂OH; n = 1-2] which have a good affinity of the NK-1 receptor and therefore they may be used in the treatment or prevention of diseases, related to this receptor, were prepd. and formulated. E.g., a multi-step synthesis of I [R₁ = [1,2,4]triazol-1-yl; R₂ = Me] which showed pK_i of 8.4 against binding at human NK1 receptors in CHO cells, was given.

ST phenylpyridine prepn neurokinin NK1 receptor antagonist

IT Human
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (type NK1; prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 393508-72-0P 393508-79-7P 393508-81-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 393508-70-8P 393508-71-9P 393508-73-1P
393508-74-2P 393508-75-3P 393508-76-4P
393508-77-5P 393508-78-6P 393508-80-0P
393508-82-2P 393508-83-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 110-91-8, Morpholine, reactions 288-32-4, Imidazole, reactions 288-88-0, 1H-1,2,4-Triazole 2799-21-5 3282-30-2, Pivaloyl chloride 3900-89-8, 2-Chlorophenylboronic acid 4023-34-1, Cyclopropanecarboxylic acid chloride 4548-45-2, 2-Chloro-5-nitropyridine 5326-23-8, 6-Chloronicotinic acid 5382-16-1, 4-Hydroxypiperidine 16419-60-6, o-Tolylboronic acid 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium chloride 86864-60-0 289686-69-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 26820-62-2P 52023-68-4P 54189-82-1P 290296-68-3P
290297-13-1P 290297-14-2P 290297-32-4P 290297-33-5P
290297-34-6P 290297-35-7P 290297-36-8P 290297-40-4P
290297-41-5P 290298-22-5P 342416-98-2P 393508-84-4P
393508-85-5P 393508-86-6P 393508-87-7P 393508-88-8P
393508-89-9P 393508-90-2P 393508-91-3P
393508-92-4P 393508-93-5P 393509-29-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Hoffmann La Roche; DE 10008042 A 2000 HCAPLUS

(2) Hosoki, R; EUROPEAN JOURNAL OF PHARMACOLOGY 1998, V341(2/3), P235 HCAPLUS

(3) Ikeura, Y; CHEMICAL AND PHARMACEUTICAL BULLETIN 1997, V45(10), P1642 HCAPLUS

(4) Natsugari, H; WO 9947132 A 1999 HCAPLUS

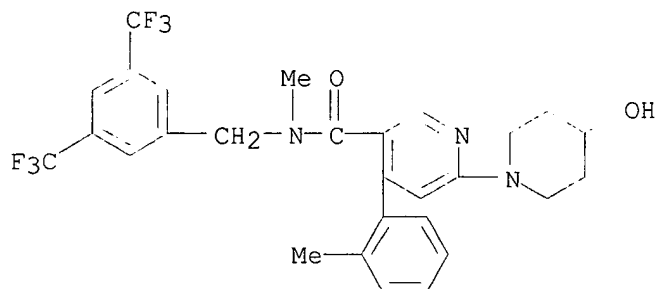
(5) Natsugari, H; JOURNAL OF MEDICINAL CHEMISTRY 1995, V38(16), P3106 HCAPLUS

IT 393508-72-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1**
receptor antagonists)

RN 393508-72-0 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-6-(4-
hydroxy-1-piperidiny)-N-methyl-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)



L118 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:72051 HCAPLUS

DN 136:118387

TI Preparation of N-oxides as NK1 receptor antagonist prodrugs of
4-phenylpyridine derivatives

IN **Hoffmann, Torsten**; Poli, Sonia Maria; Schnider, Patrick;
Sleight, Andrew

PA F. Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D213-76

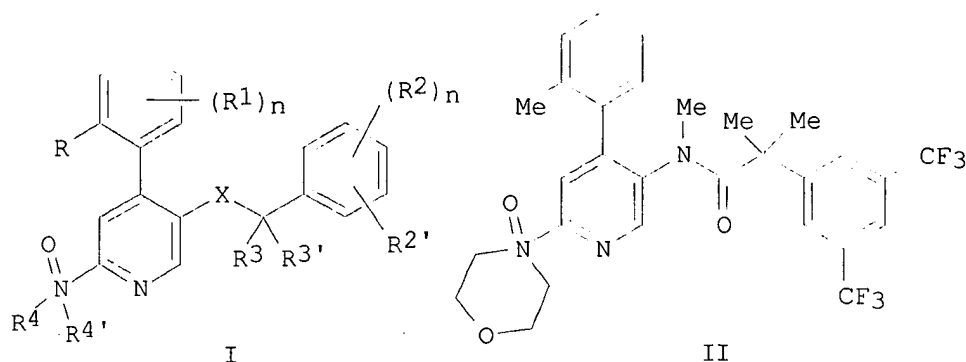
ICS C07D213-82; C07D401-04; A61K031-44; A61P025-22; A61P025-24

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002006236	A1	20020124	WO 2001-EP7850	20010709 <--
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 2002045642	A1	20020418	US 2001-904059	20010712 <--
PRAI	EP 2000-115287	A	20000714 <--		
OS	MARPAT 136:118387				
GI					



AB The prepn. is described for N-oxides (I) wherein R is hydrogen, lower alkyl, lower alkoxy, or trifluoromethyl; R1 is hydrogen or halogen; or R and R1 may be together with the ring carbon atoms to which they are attached -CH=CH-CH=CH-; R2 and R2' are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or R2 and R2' may be together -CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy; R3, R3' are independently from each other hydrogen, lower alkyl or cycloalkyl; R4, R4' are independently from each other -(CH2)mOR6 or lower alkyl; or R4 and R4' form together with the N-atom to which they are attached a cyclic tertiary amine with substituent R5 chosen from hydrogen, hydroxy, lower alkyl, -lower alkoxy, -(CH2)mOH, -COOR3, -CON(R3)2, -N(R3)CO-lower alkyl or -C(O)R3; R6 is hydrogen, lower alkyl or phenyl; X is -C(O)N(R6)-, -N(R6)C(O)-, -(CH2)mO- or -O(CH2)m-; n is 0, 1, 2, 3 or 4 and; m is 1, 2, or 3; and to their pharmaceutically acceptable acid addn. salts. These compds. may be used as prodrugs for the treatment or prevention of illnesses, related to the NK1 receptor. Thus, 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(4-oxymorpholin-4-yl)-4-o-tolylpyridin-3-yl]isobutyramide (II) and related compds. were prepd. in multistep procedures.

ST aminopyridine oxide prepn NK1 receptor antagonist prodrug;
oxymorpholinylpyridine prepn NK1 receptor antagonist prodrug

IT Tachykinin receptors

(NK1 antagonists; prepn. of N-oxides as NK1

receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 26820-62-2P 52023-68-4P 54189-82-1P 290296-68-3P
290296-70-7P 290296-71-8P 290296-73-0P
290296-74-1P 290296-75-2P 290296-76-3P
290296-77-4P 290296-83-2P 290296-85-4P
290296-87-6P 290296-89-8P 290296-90-1P
290296-91-2P 290296-92-3P 290297-00-6P
290297-01-7P 290297-02-8P 290297-03-9P
290297-04-0P 290297-05-1P 290297-06-2P
290297-07-3P 290297-08-4P 290297-10-8P
290297-11-9P 290297-32-4P 290297-33-5P 290297-34-6P
290297-35-7P 290297-36-8P 290297-39-1P 290297-53-9P
290298-21-4P 342416-98-2P 391675-02-8P
391675-03-9P 391675-11-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate product in prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 391674-73-0P 391674-74-1P 391674-75-2P
391674-76-3P 391674-77-4P 391674-78-5P
391674-79-6P 391674-80-9P 391674-81-0P
391674-82-1P 391674-83-2P 391674-84-3P

391674-85-4P 391674-86-5P 391674-87-6P
 391674-88-7P 391674-89-8P 391674-90-1P
 391674-91-2P 391674-92-3P 391674-93-4P
 391674-94-5P 391674-95-6P 391674-96-7P
 391674-97-8P 391674-98-9P 391674-99-0P
 391675-00-6P 391675-01-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 79286-87-6, 3-(Acetylmethylamino)pyrrolidine

RL: RCT (Reactant); RACT (Reactant or reagent)

(racemic; reactant for prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 86-52-2, 1-(Chloromethyl)naphthalene 109-83-1, N-Methylethanolamine
 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions
 123-90-0, Thiomorpholine 506-59-2, Dimethylamine hydrochloride
 1126-09-6, Ethyl isonipecotate 1765-40-8, 2,3,4,5,6-Pentafluorobenzyl
 bromide 2799-21-5, (R)-3-Hydroxypyrrolidine 2942-59-8,
 2-Chloronicotinic acid 3771-13-9, 2-Chloro-5-methoxybenzyl bromide
 3900-89-8, 2-Chlorophenylboronic acid 4548-45-2, 2-Chloro-5-
 nitropyridine 4670-10-4, 3,5-Dimethoxyphenylacetic acid 5382-16-1,
 4-Hydroxypiperidine 6626-23-9, 1-(Chloromethyl)-2-methylnaphthalene
 7035-02-1, 2-Methoxybenzyl chloride 7035-11-2, 5-Chloro-2-methoxybenzyl
 chloride 16419-60-6, o-Tolylboronic acid 32247-96-4,
 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium
 chloride 57260-71-6, 1-tert-Butoxycarbonylpiperazine 85068-33-3,
 3,5-Bis(trifluoromethyl)phenylacetic acid 86802-98-4,
 2-(Chloromethyl)-1,4-dimethoxynaphthalene 195447-79-1,
 3-Fluoro-5-(trifluoromethyl)phenylacetic acid 289686-69-7
290296-93-4 290297-55-1 391675-13-1

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant for prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) F Hoffmann-La Roche Ag; EP 1035115 A 2000 HCAPLUS
- (2) F Hoffmann-La Roche Ag; EP 1103545 A 2001 HCAPLUS
- (3) Ikeura, Y; CHEM PHARM BULL 1997, V45(10), P1642 HCAPLUS

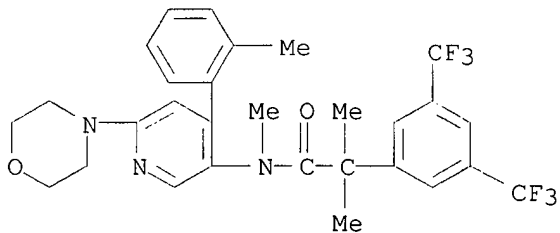
IT **290296-68-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate product in prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

RN 290296-68-3 HCAPLUS

CN Benzeneacetamide, N,.alpha.,.alpha.-trimethyl-N-[4-(2-methylphenyl)-6-(4-morpholinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)

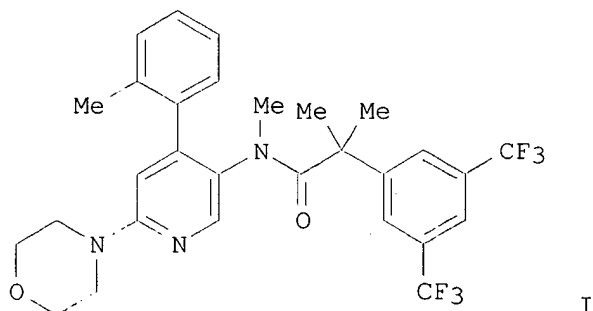


DN 135:5620
 TI Preparation of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor
 IN Ballard, Theresa Maria; Higgins, Guy Andrew; Hoffmann, Torsten; Poli, Sonia Maria; Sleight, Andrew
 PA F. Hoffmann-La Roche A.-G., Switz.
 SO Eur. Pat. Appl., 12 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 IC ICM C07D213-75
 ICS A61K031-44; A61P025-22; A61P025-24
 CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1103545	A1	20010530	EP 2000-125450	20001121 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	GB 2356863	A1	20010606	GB 2000-28566	20001123 <--
	DE 10058310	A1	20010531	DE 2000-10058310	20001124 <--
	FR 2801590	A1	20010601	FR 2000-15193	20001124 <--
	JP 2001151754	A2	20010605	JP 2000-356833	20001124 <--
	NO 2000006012	A	20010530	NO 2000-6012	20001128 <--
	BR 2000005616	A	20010717	BR 2000-5616	20001128 <--
	ES 2171134	A1	20020816	ES 2000-2839	20001128 <--
	CN 1297888	A	20010606	CN 2000-134260	20001129 <--
PRAI	EP 1999-123685	A	19991129	<--	

GI



AB The title compd. I which is a potent and selective antagonist at recombinant human neurokinin1 (NK1) receptors expressed in CHO cells, was prepd. (details of multi-step synthesis were given) and formulated. The compd. I showed an affinity (pKi) of 9.0 for the human NK1 receptor over 2 orders of magnitude of selectivity for the NK1 receptor compared to NK2 and NK3 receptors and compared to over 50 other binding sites that have been evaluated.

ST neurokinin receptor selective antagonist bistrifluoromethylphenylmethylmorpholinyltolylpyridinylisobutyramide

IT **Tachykinin receptors**
 RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
 (NK1; prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

IT 290296-68-3P 341023-51-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

IT 110-91-8, Morpholine, reactions 3282-30-2, Pivaloyl chloride
4548-45-2, 2-Chloro-5-nitropyridine 16419-60-6, o-Tolylboronic acid
289686-69-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

IT 26820-62-2P 52023-68-4P 290297-32-4P 290297-33-5P 290297-34-6P
290297-35-7P 290297-36-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Glaxo Group Ltd; EP 0916346 A 1999 HCAPLUS

(2) La Roche, H; EP 1035115 A 2000 HCAPLUS

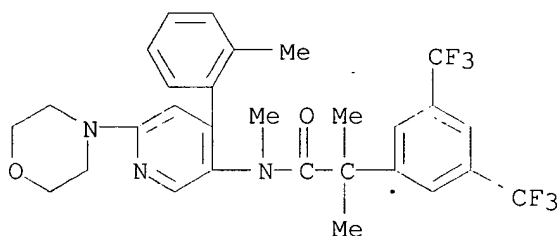
IT 290296-68-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

RN 290296-68-3 HCAPLUS

CN Benzeneacetamide, N,.alpha.,.alpha.-trimethyl-N-[4-(2-methylphenyl)-6-(4-morpholinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)



L118 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 2000:607348 HCAPLUS

DN 133:207811

TI Preparation of N-benzyl-4-tolylnicotinamides and related compounds as **neurokinin-1 receptor antagonists**.

IN Boes, Michael; Branca, Quirico; Galley, Guido; Godel, Thierry; Hoffmann, Torsten; Hunkeler, Walter; Schnider, Patrick; Stadler, Heinz

PA F. Hoffmann-La Roche Ag, Switz.

SO Ger. Offen., 38 pp.

CODEN: GWXXBX

DT Patent

LA German

IC ICM C07D213-82

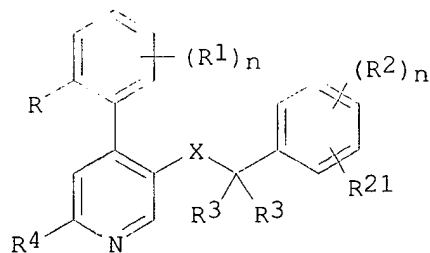
ICS C07D213-36; C07D213-22; C07D401-02; A61K031-4406

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 28

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10008042	A1	20000831	DE 2000-10008042	20000222 <--
	EP 1035115	A1	20000913	EP 2000-102260	20000215 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	GB 2347422	A1	20000906	GB 2000-3908	20000218 <--
	FR 2790473	A1	20000908	FR 2000-2170	20000222 <--
	US 6297375	B1	20011002	US 2000-507456	20000222 <--
	ZA 2000000894	A	20000824	ZA 2000-894	20000223 <--
	NO 2000000885	A	20000825	NO 2000-885	20000223 <--
	BR 2000000908	A	20000912	BR 2000-908	20000223 <--
	CN 1270959	A	20001025	CN 2000-102401	20000223 <--
	ES 2171109	A1	20020816	ES 2000-418	20000223 <--
	JP 2000247957	A2	20000912	JP 2000-47003	20000224 <--
	US 2002091265	A1	20020711	US 2001-901982	20010710 <--
	US 6479483	B2	20021112		
PRAI	EP 1999-103504	A	19990224 <--		
	EP 1999-123689	A	19991129 <--		
	US 2000-507456	A3	20000222 <--		
OS	MARPAT 133:207811				
GI					



I

AB Title compds. [I; R = H, alkyl, alkoxy, halo, CF₃; R₁ = H, halo; RR₁ = CH:CHCH:CH; R₂, R₂₁ = H, halo, CF₃, alkoxy, cyano; R₂R₂₁ = (substituted) CH:CHCH:CH; R₃ = H, alkyl, cycloalkyl; R₄ = H, N(R₅)₂, N(R₅)(CH₂)_nOH, N(R₅)S(O)₂A, N(R₅)S(O)₂Ph, N:CHN(R₅)₂, N(R₅)C(O)R₅, specified cyclic tertiary amine; R₅ = H, cycloalkyl, benzyl, alkyl; X = C(O)N(R₅), (CH₂)_mO, (CH₂)_mN(R₅), N(R₅)C(O), N(R₅)(CH₂)_m; n = 0-4; m = 1, 2], were prepd. Thus, 4-o-tolylnicotinic acid (prepn. given) was stirred with SOCl₂ and cat. DMF in CH₂Cl₂ to give a residue which was refluxed with N-[3,5-bis(trifluoromethyl)benzyl]-N-methylamine and Et₃N in PhMe to give 67% N-(3,5-bistrifluoromethylbenzyl)-N-methyl-4-o-tolylnicotinamide. Tested I **antagonized NK-1 receptors** with pK_i = 8.20-9.54.

ST benzyltolylnicotinamide prepn neurokinin antagonist; nicotinamide benzyl tollyl prepn neurokinin antagonist

IT **Tachykinin receptors**

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(NK1, antagonists; prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**)

IT 290297-14-2P 290297-18-6P 290297-26-6P
290297-30-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as
neurokinin-1 receptor antagonists

)

IT 290296-41-2P 290296-42-3P 290296-43-4P
290296-44-5P 290296-45-6P 290296-46-7P
290296-47-8P 290296-48-9P 290296-49-0P
290296-50-3P 290296-51-4P 290296-52-5P
290296-53-6P 290296-54-7P 290296-55-8P
290296-56-9P 290296-57-0P 290296-58-1P
290296-59-2P 290296-60-5P 290296-61-6P
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290298-21-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as
neurokinin-1 receptor antagonists

)

IT 86-52-2, 1-Chloromethylnaphthalene 98-09-9, Benzenesulfonyl chloride
98-80-6, Phenylboronic acid 107-14-2, Chloroacetonitrile 109-01-3,
1-Methylpiperazine 109-83-1, N-Methylethanolamine 110-91-8,
Morpholine, reactions 123-90-0, Thiomorpholine 124-63-0,
Methanesulfonyl chloride 501-53-1 540-51-2, 2-Bromoethanol 628-89-7,
2-(2-Chloroethoxy)ethanol 653-35-0, 2,3,4,5,6-Pentafluorobenzyl chloride
1126-09-6, Ethyl isonipecotate 1423-27-4 1993-03-9 2506-41-4,
2-Chloromethylnaphthalene 2799-21-5 2942-59-8, 2-Chloronicotinic acid
3900-89-8 4548-45-2, 2-Chloro-5-nitropyridine 4670-10-4,
3,5-Dimethoxyphenylacetic acid 5382-16-1, 4-Hydroxypiperidine
5720-06-9, o-Methoxyphenylboronic acid 6626-23-9,
1-Chloromethyl-2-methylnaphthalene 7035-02-1, 2-Methoxybenzyl chloride
7035-11-2, 5-Chloro-2-methoxybenzyl chloride 16419-60-6, o-Tolylboronic
acid 20980-22-7, 2-(1-Piperazinyl)pyrimidine 21867-64-1,
1-Propylpiperazine 32247-96-4 33872-80-9, o-Tolylmagnesium chloride
40004-08-8, 1-Ethoxycarbonylmethylpiperazine 41239-40-1 50893-53-3
51791-12-9, 3-Chloromethyl-1,2,4-oxadiazole 57260-71-6,
1-tert-Butoxycarbonylpiperazine 63592-85-8, Methyl 4-chloronicotinate
70298-88-3 79286-87-6 85068-33-3 86802-98-4 90390-21-9
90390-28-6 101079-83-8, 2-Chloro-5-methoxybenzyl chloride 139911-29-8,
4-Fluoro-2-methylphenylboronic acid 155742-64-6 159820-24-3
195447-79-1 201345-08-6 289686-69-7 290297-42-6 290297-43-7

290297-44-8 290297-45-9 290297-46-0 **290297-47-1**
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 290297-53-9 290297-54-0 290297-55-1 290297-56-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as
neurokinin-1 receptor antagonists

IT 26820-62-2P 54189-82-1P 54864-91-4P 55403-34-4P 105812-87-1P
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 290298-22-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as
neurokinin-1 receptor antagonists

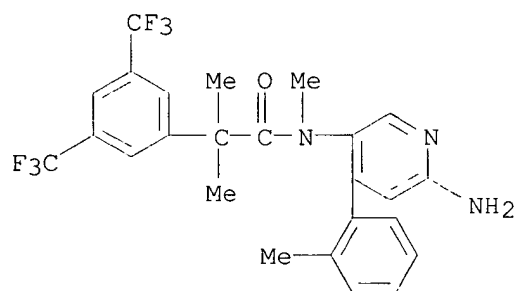
IT **290297-14-2P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT
 (Reactant or reagent); USES (Uses)

(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as
neurokinin-1 receptor antagonists

RN 290297-14-2 HCAPLUS

CN Benzeneacetamide, N-[6-amino-4-(2-methylphenyl)-3-pyridinyl]-
 N,.alpha.,.alpha.-trimethyl-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX
 NAME)



L118 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:613656 HCAPLUS

DN 131:228734

TI Preparation of diazocinonaphthyridines, diazepinonaphthyridines, and
 related compounds having tachykinin receptor antagonistic activity for
 preventing or treating depression, anxiety, manic-depressive illness or
 psychopathy.

IN Natsugari, Hideaki; Doi, Takayuki; Ikeura, Yoshinori

PA Takeda Chemical Industries, Ltd., Japan

SO PCT Int. Appl., 207 pp.

CODEN: PIXXD2

DT Patent

LA English

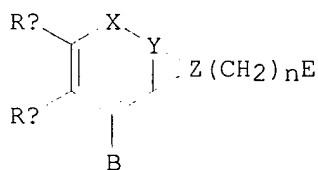
IC ICM A61K031-00

CC 28-23 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 1

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PI	WO 9947132	A2	19990923	WO 1999-JP1358	19990318	<--
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	US 2002132817	A1	20020919	US 2002-97791	20020313	<--
PRAI	JP 1998-69999	A	19980319	<--		
	EP 1999-909233	A3	19990318	<--		
	WO 1999-JP1358	W	19990318	<--		
	US 1999-308311	A1	19990518	<--		
OS	MARPAT 131:228734					
GI						



- AB Pharmaceutical compns. for preventing or treating depression, anxiety, manic-depression, or psychopathy [I; XY = N:C, CON, CSN; Ra, Rb = H, substituent; RaRb = atoms to form a (substituted) (heterocyclic) ring; B, E = (substituted) homocyclic or heterocyclic ring, Z = (substituted) N-contg. heterocyclic ring; n = 1-6; with provisos], are claimed. Thus, (9R)-7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9,10,11-hexahydro-9-methyl-5-(4-methylphenyl)-6,13-dioxo-13H-[1,4]-diazocino[2,1-g][1,7]naphthyridine (II) (prepn. described) antagonized substance P with IC50 = 0.43 nM. A II tablet formulation is given.
- ST diazocinonaphthyridine diazepinonaphthyridine prepn tachykinin receptor antagonist; arthritis treatment diazocinonaphthyridine diazepinonaphthyridine; pain treatment diazocinonaphthyridine diazepinonaphthyridine; cough treatment diazocinonaphthyridine diazepinonaphthyridine; psychopathy treatment diazocinonaphthyridine diazepinonaphthyridine; anxiety treatment diazocinonaphthyridine diazepinonaphthyridine; depression treatment diazocinonaphthyridine diazepinonaphthyridine
- IT **Tachykinin receptors**
 RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
 (antagonists; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor

antagonistic activity)

IT Intestine, disease
(irritable bowel syndrome, treatment; prepn. of
diazocinonaphthyridines, diazepinonaphthyridines, and related compds.
having tachykinin receptor antagonistic activity)

IT Mental disorder
(manic bipolar disorder, treatment; prepn. of diazocinonaphthyridines,
diazepinonaphthyridines, and related compds. having tachykinin receptor
antagonistic activity)

IT Analgesics
Antiarthritics
Antiasthmatics
Antidepressants
Antiemetics
Antipsychotics
Antitussives
Anxiolytics
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and
related compds. having tachykinin receptor antagonistic activity)

IT 33507-63-0, Substance P **86933-74-6**, Neurokinin A
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
(Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of diazocinonaphthyridines,
diazepinonaphthyridines, and related compds. having tachykinin receptor
antagonistic activity)

IT 207606-22-2P 207606-26-6P
RL: BAC (Biological activity or effector, except adverse); BPN
(Biosynthetic preparation); BSU (Biological study, unclassified); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and
related compds. having tachykinin receptor antagonistic activity)

IT 183145-60-0P 183549-77-1P 183549-78-2P 183549-79-3P 183549-80-6P
183549-81-7P 183549-82-8P 183549-83-9P 183549-84-0P 183549-85-1P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 67-63-0, Isopropanol, reactions 74-89-5, Methylamine, reactions
 74-93-1, Methyl mercaptan, reactions 100-46-9, Benzylamine, reactions
 102-49-8, 3,4-Dichlorobenzylamine 104-63-2 106-38-7, 4-Bromotoluene
 108-24-7, Acetic anhydride 109-01-3, N-Methylpiperazine 124-40-3,
 reactions 141-43-5, 2-Aminoethanol, reactions 156-87-6 616-30-8,
 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0,
 Diethyl bromomalonate 699-98-9, 2,3-Pyridinedicarboxylic anhydride
 765-30-0, Cyclopropanamine 2508-29-4, 5-Amino-1-pentanol 3858-80-8,
 3,5-Dimethylbenzylamine 4637-24-5, DMF dimethyl acetal 6850-57-3,
 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl
 hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine
 24687-79-4 26543-05-5 34967-24-3, 3,5-Dimethoxybenzylamine
 39989-43-0, 3,5-Dichlorobenzylamine 40172-02-9 40172-06-3
 41236-20-8, 3-Bromopropylamine hydrochloride 44565-27-7,
 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic
 acid 74975-27-2 80657-57-4 85068-29-7, 3,5-
 Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-
 propanol 91692-76-1 104154-93-0 110239-06-0, Diethyl
 4-phenyl-2,3-pyridinedicarboxylate 122853-70-7 147078-78-2
 183551-06-6 183551-17-9 183551-51-1 183551-52-2 183551-53-3
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RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT **86933-74-6**, Neurokinin A

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

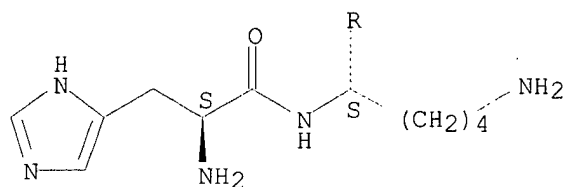
(antagonists; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

RN 86933-74-6 HCAPLUS

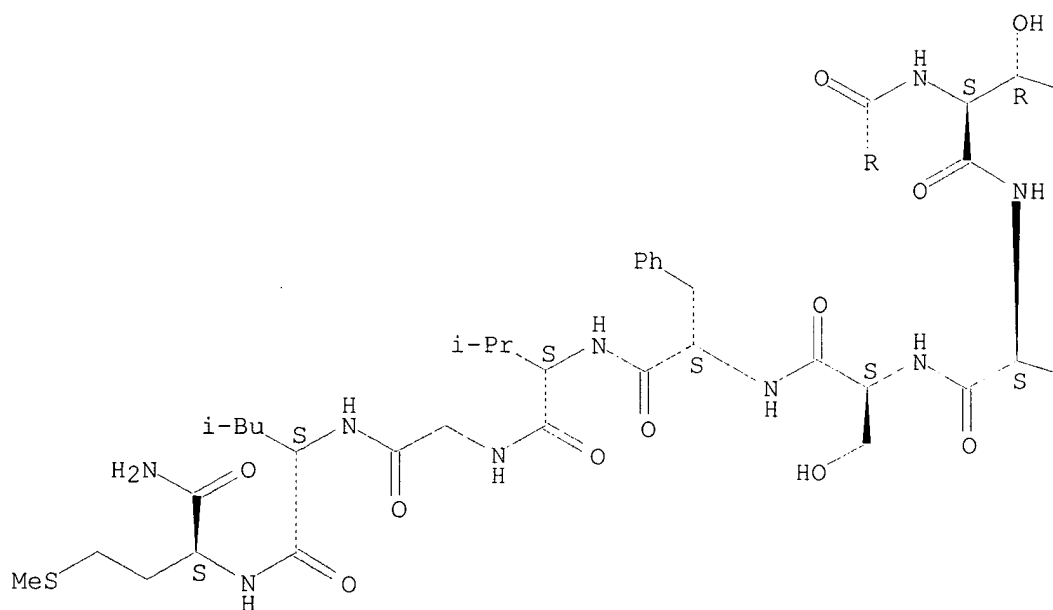
CN Neurokinin A (swine spinal cord) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



PAGE 2-B

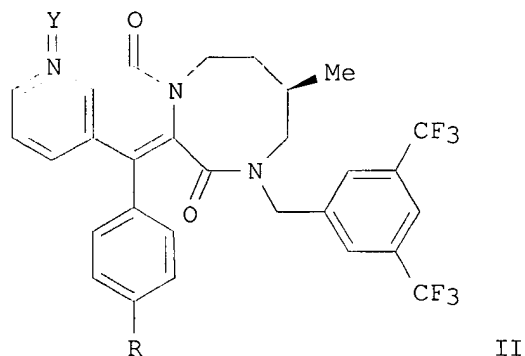
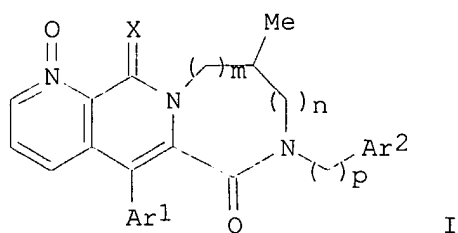
Me

CO₂H

TI Preparation of medium-ring polycyclic heterocycles as tachykinin receptor antagonists
 IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki; Ikeura, Yoshinori; Kimura, Chiharu; Tarui, Naoki
 PA Takeda Chemical Industries, Ltd., Japan
 SO U.S., 66 pp., Cont.-in-part of U.S. Ser. No. 621,360.
 CODEN: USXXAM
 DT Patent
 LA English
 IC ICM A61K031-33
 ICS A61K031-55; C07D245-00; C07D487-00
 NCL 514183000
 CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1

FAN.CNT 3

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	US 5786352	A	19980728	US 1996-621360	19960325 <--
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OS	MARPAT 129:95515				
GI					



- AB A variety of polycyclic heterocycles are disclosed, and in particular the compds. I and salts are claimed [wherein X = O, S; Ar1, Ar2 = certain (un)substituted Ph; m, n = 0 to 4; (m+n) = 2 to 4; p = 1 to 6]. The compds. show an excellent tachykinin receptor antagonistic effect. For instance, (9R)-7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9,10,11-hexahydro-9-methyl-5-(4-methylphenyl)-6,13-dioxo-13H-[1,4]diazocino[2,1-g][1,7]naphthyridine, i.e., II [Y = absent, R = Me] (prepn. given) underwent hydroxylation by Streptomyces subrutilus IFO 13388 to give II [Y = absent, R = CH2OH] (III). The latter underwent acetylation with Ac2O and pyridine, N-oxidn. with m-ClC6H4C(O)OOH, and hydrolytic deacetylation, to give title compd. II [Y = O, R = CH2OH]. III had an ID50 of 2.5 .mu.g/kg i.v. for inhibiting capsaicin-induced tracheal plasma extravasation in anesthetized guinea pigs. I also showed substance P receptor antagonistic and NK2 receptor inhibitory activities.
- ST heterocyclic prepn tachykinin receptor antagonist; diazocinonaphthyridine prepn substance P receptor antagonist
- IT **Tachykinin receptors**
(NK1 antagonists; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)
- IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK1, treatment of mediated diseases; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)
- IT **Tachykinin receptors**
(NK2 antagonists; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)
- IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK2, treatment of mediated diseases; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)
- IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(treatment of mediated diseases; prepn. of medium-ring polycyclic

heterocycles as tachykinin receptor antagonists)

IT 207606-22-2P 207606-26-6P
 RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 183145-60-0P 183549-77-1P 183549-78-2P 183549-79-3P 183549-80-6P
 183549-81-7P 183549-82-8P 183549-83-9P 183549-84-0P 183549-85-1P
 183549-86-2P 183549-87-3P 183549-88-4P 183549-89-5P 183549-90-8P
 183549-91-9P 183549-92-0P 183549-93-1P 183549-94-2P 183549-95-3P
 183549-96-4P 183549-97-5P 183549-98-6P 183550-00-7P 183550-02-9P
 183550-03-0P 183550-05-2P 183550-07-4P 183550-08-5P 183550-09-6P
 183550-10-9P 183550-11-0P 183550-13-2P 183550-15-4P 183550-16-5P
 183550-18-7P 183550-20-1P 183550-21-2P 183550-23-4P 183550-26-7P
 183550-27-8P 183550-29-0P 183550-31-4P 183550-32-5P 183550-33-6P
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 183550-39-2P 183550-40-5P 183550-41-6P 183550-42-7P 183550-43-8P
 183550-44-9P 183550-45-0P 183550-46-1P 183550-47-2P 183550-48-3P
 183550-49-4P 183550-50-7P 183550-51-8P 183550-52-9P 183550-53-0P
 183550-54-1P 183550-55-2P 183550-56-3P 183550-57-4P 183550-58-5P
 183550-59-6P 183550-60-9P 183550-61-0P 183550-62-1P 183550-63-2P
 183550-64-3P 183550-65-4P 183550-66-5P 183550-67-6P 183550-68-7P
 183550-69-8P 183550-70-1P 207606-24-4P 207606-31-3P 207606-34-6P
 209672-70-8P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 67-63-0, Isopropanol, reactions 100-46-9, Benzylamine, reactions 102-49-8, 3,4-Dichlorobenzylamine 104-63-2, N-(2-Hydroxyethyl)benzenemethanamine 106-38-7, 4-Bromotoluene 109-01-3, 1-Methylpiperazine 109-73-9, n-Butylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 156-87-6, 3-Amino-1-propanol 616-30-8, 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0, Diethyl bromomalonate 699-98-9, Pyridine-2,3-dicarboxylic acid anhydride 765-30-0, Cyclopropylamine 2508-29-4, 5-Amino-1-pentanol 5003-71-4 6850-57-3, 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine 24687-79-4 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 34967-24-3, 3,5-Dimethoxybenzylamine 40172-02-9 40172-06-3 44565-27-7, 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic acid 74975-27-2, 4-(4-Methylbenzoyl)-3-pyridinecarboxylic acid 80657-57-4 85068-29-7, 3,5-Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-propanol 104154-93-0 110239-06-0, Diethyl 4-phenyl-2,3-pyridinedicarboxylate 147078-78-2, 2-Chloro-4-phenyl-3-pyridinecarboxylic acid 183551-51-1, 3,5-Bis(trifluoromethyl)benzyl methanesulfonate 183551-52-2 183551-53-3 183551-54-4 183551-55-5 183551-69-1 183551-70-4 183551-71-5 183812-31-9
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 110171-23-8P 116060-91-4P 147078-85-1P 156241-24-6P 183550-71-2P
 183550-72-3P 183550-73-4P 183550-74-5P 183550-75-6P 183550-76-7P
 183550-77-8P 183550-78-9P 183550-79-0P 183550-80-3P 183550-81-4P
 183550-82-5P 183550-83-6P 183550-84-7P 183550-85-8P 183550-86-9P
 183550-87-0P 183550-88-1P 183550-89-2P 183550-90-5P 183550-91-6P
 183550-92-7P 183550-93-8P 183550-94-9P **183550-95-0P**
 183550-96-1P 183550-97-2P 183550-98-3P 183550-99-4P 183551-00-0P

183551-01-1P 183551-02-2P 183551-03-3P 183551-04-4P
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183551-24-8P 183551-25-9P 183551-26-0P
183551-27-1P 183551-28-2P 183551-29-3P
183551-30-6P 183551-31-7P 183551-32-8P
183551-33-9P 183551-34-0P 183551-35-1P
183551-36-2P 183551-37-3P 183551-38-4P 183551-39-5P
183551-40-8P 183551-41-9P 183551-42-0P 183551-43-1P 183551-44-2P
183551-45-3P 183551-46-4P 183551-47-5P 183551-48-6P
183551-49-7P 183551-50-0P 183551-56-6P
183551-57-7P 183551-58-8P 183551-59-9P 183551-60-2P
183551-61-3P 183551-62-4P 183551-63-5P 183551-64-6P
183551-65-7P 183551-66-8P 183551-67-9P 183551-68-0P
183551-72-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor
antagonists)

IT 33507-63-0, Substance P

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
(Miscellaneous); BIOL (Biological study); PROC (Process)

(treatment of mediated diseases; prepn. of medium-ring polycyclic
heterocycles as tachykinin receptor antagonists)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

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- (2) Anon; DE 2617101 1977 HCAPLUS
- (3) Anon; DE 2638828 1978 HCAPLUS
- (4) Anon; DE 2722416 1978 HCAPLUS
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3',4'-e]-Pyridine Series From 1-Benzylidene-2,3-Dioxopyrrolidines 1982,
P603 HCAPLUS
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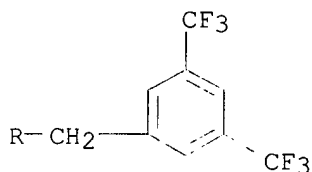
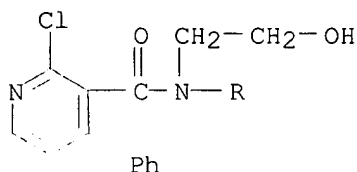
IT 183550-95-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor
antagonists)

RN 183550-95-0 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-2-chloro-
N-(2-hydroxyethyl)-4-phenyl- (9CI) (CA INDEX NAME)



L118 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:706935 HCAPLUS

DN 128:3591

TI Potent NK1 receptor antagonists: synthesis and antagonistic activity of various heterocycles with an N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoyl substituent

AU Ikeura, Yoshinori; Tanaka, Toshimasa; Kiyota, Yutaka; Morimoto, Shinji; Ogino, Masaki; Ishimaru, Takenori; Kamo, Izumi; Doi, Takayuki; Natsugari, Hideaki

CS Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., Osaka, 532, Japan

SO Chemical & Pharmaceutical Bulletin (1997), 45(10), 1642-1652

CODEN: CPBTAL; ISSN: 0009-2363

PB Pharmaceutical Society of Japan

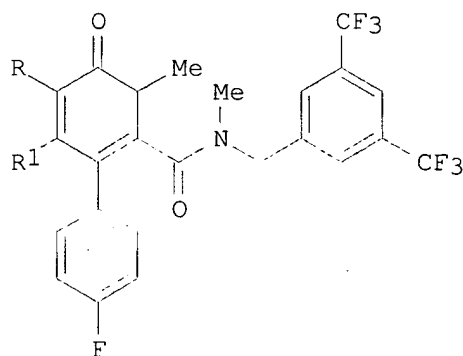
DT Journal

LA English

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1

GI



I

AB Various N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoyl heterocycles modified at rings A and B in the isoquinolone and pyrido[3,4-b]pyridine nuclei were prepd. and evaluated for NK1 receptor antagonistic activities. The structure-activity relationship studies on this series, along with conformational anal., showed that for ring A, 6-membered heterocycles are preferable to 5-membered heterocycles (a ca. 300-fold difference in potency), the 6-membered ring seems to function as an anchor by fixing the

pendant Ph group in a desirable orientation for receptor binding, and since compds. with arom. rings and those with aliph. rings as ring B both show good potency, this ring does not seem to be essential for receptor recognition. Among the compds. synthesized, the tetrahydropyridine derivs. I [RR1 = NMe(CH₂)₃, CH₂NMeCH₂CH₂, (CH₂)₃NMe] exhibited excellent inhibitory effects both in vitro and in vivo, with potent activity upon oral administration (ED₅₀-0.20-0.27 mg/kg) (capsaicin-induced plasma extravasation in guinea pig trachea).

ST trifluoromethylbenzylcarbamoynaphthyridine prepn NK1 receptor antagonist;
naphthyridine trifluoromethylbenzylcarbamoynl prepn NK1 receptor antagonist

IT **Tachykinin receptors**

(NK1 antagonists; prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

IT 159817-70-6

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

IT 168541-21-7P 168541-28-4P 168541-66-0P 168541-83-1P 168541-85-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

IT 159818-48-1P 168541-26-2P 168541-29-5P 168541-33-1P 168541-38-6P

168541-45-5P 168541-46-6P 168541-82-0P 198878-46-5P

198878-48-7P 198878-50-1P 198878-53-4P 198878-55-6P

198878-56-7P 198878-57-8P 198878-76-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

IT 699-98-9, 2,3-Pyridinedicarboxylic anhydride 4664-08-8,
3,4-Pyridinedicarboxylic anhydride 6007-83-6, 2,3-Thiophenedicarboxylic anhydride 6007-85-8, 3,4-Thiophenedicarboxylic anhydride 17684-12-7
25808-30-4, N-Methylaminoacetonitrile hydrochloride 52605-49-9,
Sarcosine ethyl ester hydrochloride 85068-29-7 85679-03-4
125064-63-3 159820-24-3 168543-12-2, 1-Methyl-2,3-pyrroledicarboxylic anhydride 198878-62-5 198878-64-7 198878-67-0 198878-68-1
198878-70-5 198878-82-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

IT 122853-76-3P 122853-77-4P 122853-81-0P 168541-34-2P 168542-03-8P

168542-04-9P 168542-05-0P 168542-06-1P 168542-07-2P 168542-11-8P

168542-18-5P 168542-19-6P 168542-21-0P 168542-22-1P 168542-23-2P

168542-24-3P 168542-25-4P 168542-28-7P 168542-32-3P 168542-36-7P

168542-40-3P 168542-44-7P 168542-45-8P 168542-46-9P 168542-51-6P

168542-52-7P 168542-53-8P 168542-54-9P 168543-10-0P 198878-60-3P

198878-71-6P 198878-72-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoynlpyridinone analogs as potent NK1 receptor antagonists)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

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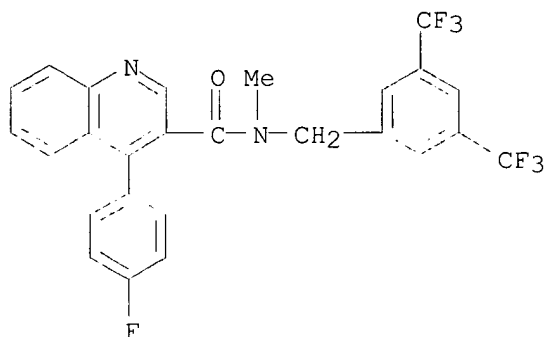
IT 198878-48-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

RN 198878-48-7 HCAPLUS

CN 3-Quinolinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-4-(4-fluorophenyl)-N-methyl- (9CI) (CA INDEX NAME)



L118 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:728630 HCAPLUS

DN 126:8145

TI Preparation of polycyclic heterocycles as tachykinin receptor antagonists

IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki; Ikeura, Yoshinori; Kimura, Chiharu

PA Takeda Chemical Industries, Ltd., Japan

SO Eur. Pat. Appl., 94 pp.

CODEN: EPXXDW

DT Patent

LA English

IC ICM C07D471-14

ICS A61K031-495; C07D498-04; C07D471-04; C07D487-04

CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 733632	A1	19960925	EP 1996-104500	19960321 <--
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	NO 9601160	A	19960925	NO 1996-1160	19960321 <--
	TW 394773	B	20000621	TW 1996-85103427	19960321 <--
	CA 2172421	AA	19960925	CA 1996-2172421	19960322 <--
	AU 9648261	A1	19961003	AU 1996-48261	19960322 <--
	AU 699611	B2	19981210		
	CN 1140172	A	19970115	CN 1996-106081	19960323 <--
	IL 117631	A1	20001121	IL 1996-117631	19960324 <--
	BR 9601125	A	19980106	BR 1996-1125	19960325 <--
	SG 69968	A1	20000125	SG 1996-6546	19960325 <--
	US 6489315	B1	20021203	US 2000-644306	20000823 <--
PRAI	JP 1995-91436	A	19950324 <--		
	JP 1995-207553	A	19950720 <--		
	JP 1995-264727	A	19950918 <--		
	JP 1996-30033	A	19960123 <--		
	US 1996-621360	A3	19960325 <--		
	US 1998-87894	A3	19980601 <--		
OS	MARPAT 126:8145				
GI	For diagram(s), see printed CA Issue.				
AB	Title compds. [I; R = (CH ₂) _n R ₄ ; R ₁ , R ₂ = H or a substituent; R ₁ R ₂ = atoms to complete a (hetero)cyclic ring; ring B = heterocyclic ring; R ₃ , R ₄ = (hetero)cyclic ring; X-Y = N:C, C(O)N, C(S)N; n = 1-6] were prep'd. Thus, 4-BrC ₆ H ₄ Me was condensed with 2,3-pyridinedicarboxylic acid and the product amidated by HN(CH ₂ CN) ₂ to give, after cyclization in 5 addnl. steps, 7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9-tetrahydro-5-(4-methylphenyl)-6,11-dioxo-11H-pyrazino[2,1-g][1,7]naphthyridine. Data for in vitro biol. activity of selected I were given.				
ST	heterocyclic prepn tachykinin receptor antagonist				
IT	Tachykinin receptors				
	RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)				
	(NK ₂ , mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)				
IT	Tachykinin receptors				
	RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)				
	(mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)				
IT	33507-63-0, Substance P				
	RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)				
	(mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)				
IT	183145-60-0P	183549-77-1P	183549-78-2P	183549-79-3P	183549-80-6P
	183549-81-7P	183549-82-8P	183549-83-9P	183549-84-0P	183549-85-1P
	183549-86-2P	183549-87-3P	183549-88-4P	183549-89-5P	183549-90-8P
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183550-69-8P	183550-70-1P			

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

IT 67-63-0, Isopropanol, reactions 100-46-9, Benzylamine, reactions 102-49-8, 3,4-Dichlorobenzylamine 104-63-2, N-(2-Hydroxyethyl)benzenemethanamine 106-38-7, 4-Bromotoluene 109-01-3, 1-Methylpiperazine 109-73-9, n-Butylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 156-87-6, 3-Amino-1-propanol 616-30-8, 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0, Diethyl bromomalonate 699-98-9, Pyridine-2,3-dicarboxylic acid anhydride 765-30-0, Cyclopropylamine 2508-29-4, 5-Amino-1-pentanol 5003-71-4 6850-57-3, 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine 24687-79-4 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 34967-24-3, 3,5-Dimethoxybenzylamine 40172-02-9 40172-06-3 44565-27-7, 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic acid 74975-27-2, 4-(4-Methylbenzoyl)-3-pyridinecarboxylic acid 85068-29-7, 3,5-Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-propanol 104154-93-0 110239-06-0, Diethyl 4-phenyl-2,3-pyridinedicarboxylate 147078-78-2, 2-Chloro-4-phenyl-3-pyridinecarboxylic acid 183551-51-1, 3,5-Bis(trifluoromethyl)benzyl methanesulfonate 183551-52-2 183551-53-3 183551-54-4 183551-55-5 183551-69-1 183551-70-4 183551-71-5 183812-31-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

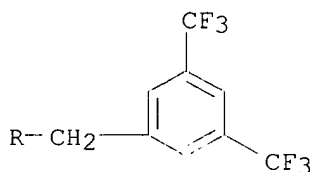
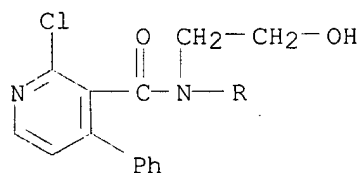
(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

IT 183550-95-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

RN 183550-95-0 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-2-chloro-
N-(2-hydroxyethyl)-4-phenyl- (9CI) (CA INDEX NAME)

L118 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1995:835514 HCAPLUS

DN 123:256684

TI Preparation of pyridopyridinecarboxamides, thienopyridinecarboxamides, and
related compounds as tachykinin antagonists and inhibitors of plasma
extravasation.

IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki

PA Takeda Chemical Industries, Ltd., Japan

SO Eur. Pat. Appl., 72 pp.

CODEN: EPXXDW

DT Patent

LA English

IC ICM C07D471-04

ICS C07D495-04; C07D513-04; C07D401-04; C07D409-04; A61K031-33;

A61K031-47

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 652218	A1	19950510	EP 1994-117576	19941108 <--
	EP 652218	B1	20010711		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	NO 9404252	A	19950511	NO 1994-4252	19941108 <--
	AT 203024	E	20010715	AT 1994-117576	19941108 <--
	CA 2135440	AA	19950511	CA 1994-2135440	19941109 <--
	FI 9405281	A	19950511	FI 1994-5281	19941109 <--
	AU 9477738	A1	19950518	AU 1994-77738	19941109 <--
	AU 678295	B2	19970522		
	BR 9404403	A	19950718	BR 1994-4403	19941109 <--
	JP 08067678	A2	19960312	JP 1994-274699	19941109 <--
	RU 2135471	C1	19990827	RU 1994-40174	19941109 <--
	HU 68810	A2	19950519	HU 1994-3230	19941110 <--
	CN 1107476	A	19950830	CN 1994-113866	19941110 <--

CN 1052004 B 20000503
 US 5585385 A 19961217 US 1994-338762 19941110 <--
 BR 9501976 A 19960430 BR 1995-1976 19950509 <--
 PRAI JP 1993-281178 A 19931110 <--
 JP 1993-337488 A 19931228 <--
 JP 1994-33637 A 19940303 <--
 JP 1994-138551 A 19940621 <--
 OS MARPAT 123:256684
 GI For diagram(s), see printed CA Issue.
 AB Title compds. [I; ring A, ring B = (substituted) homo- or heterocyclyl, .gtoreq.1 of them = (substituted) heterocyclyl; ring C = (substituted) benzene ring; R = H, (substituted) hydrocarbyl; 1 of X, Y = NR1, O; the other = CO, CS; or 1 of them = N: and the other = :CR2; R1 = H, (substituted) hydrocarbyl; R2 = H, halo, (substituted) hydrocarbyl, amino, OH; n = 1, 2], were prepd. Thus, 5-(4-fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-b]pyridinecarboxylic acid (prepn. given) was refluxed with SOCl2 in benzene and ther residue in THF was refluxed with N-[3,5-bis(trifluoromethyl)benzyl]methylamine and Et3N to give N-[3,5-bis(trifluoromethyl)benzyl]-5-(4-fluorophenyl)-7,8-dihydro-N,7-di methyl-8-oxo-6-pyrido[3,4-b]pyridinecarboxamide (II). II inhibited substance P binding to IM-9 human lymphoblasts with IC50 = 0.08 nM. Tablets contg. II were prepd.
 ST pyridopyridinecarboxamide prepn tachykinin antagonist; plasma extravasation inhibitor pyridopyridinecarboxamide; thienopyridinecarboxamide prepn plasma extravasation inhibitor
 IT Plasma
 (extravasation; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)
 IT Urinary tract
 (treatment of disorders of micturition; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)
 IT **Kinins (animal hormones)**
 RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
 (**tachykinins**, antagonists; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)
 IT 168541-32-0P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (4prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)
 IT 33507-63-0, Substance P
 RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
 (antagonists; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)
 IT 168541-17-1P 168541-18-2P 168541-19-3P 168541-20-6P 168541-21-7P
 168541-22-8P 168541-23-9P **168541-24-0P** 168541-25-1P
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168541-62-6P	168541-63-7P	168541-64-8P	168541-65-9P	168541-66-0P
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168541-72-8P	168541-73-9P	168541-74-0P	168541-75-1P	168541-76-2P
168541-77-3P	168541-78-4P	168541-79-5P	168541-80-8P	168541-81-9P
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168541-92-2P	168543-19-9P	168543-20-2P		

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 71-43-2, Benzene, reactions 74-88-4, Methyl iodide, reactions 74-89-5, Methylamine, reactions 85-44-9, 1,3-Isobenzofurandione 87-13-8, Diethyl ethoxymethylenemalonate 95-46-5, 2-Bromotoluene 100-58-3, Phenylmagnesium bromide 105-53-3 106-38-7, 4-Bromotoluene 108-86-1, Bromobenzene, reactions 110-02-1, Thiophene 122-07-6, Methylaminoacetaldehyde dimethyl acetal 460-00-4, 1-Bromo-4-fluorobenzene 462-06-6, Fluorobenzene 699-98-9, 2,3-Pyridinedicarboxylic anhydride 931-50-0, Cyclohexylmagnesium bromide 932-31-0, 2-Methylphenylmagnesium bromide 4640-67-9, 4-Fluorobenzoylacetonitrile 4664-08-8, 3,4-Pyridinedicarboxylic anhydride 4744-50-7, 2,3-Pyrazinedicarboxylic anhydride 5664-52-8, 4,5-Thiazoledicarboxylic anhydride 6007-83-6, 2,3-Thiophenedicarboxylic anhydride 6007-85-8, 3,4-Thiophenedicarboxylic anhydride 13139-86-1, 4-Methoxyphenylmagnesium bromide 25808-30-4, N-Methylaminoacetonitrile hydrochloride 28987-79-3, 3-Methylphenylmagnesium bromide 32247-96-4, 3,5-Bistrifluoromethyl benzyl bromide 40018-26-6, 2,5-Dihydroxy-1,4-dithiane 42471-56-7, 2-(2-Aminobenzoyl)pyridine 52605-49-9, N-Methylglycine ethyl ester hydrochloride 116060-91-4 159820-24-3 168543-12-2, 1-Methylpyrrole-2,3-dicarboxylic anhydride

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT	30006-03-2P	40298-32-6P	46496-80-4P	74975-25-0P	74975-27-2P
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	168542-38-9P	168542-39-0P	168542-40-3P	168542-41-4P	168542-42-5P
	168542-43-6P	168542-44-7P	168542-45-8P	168542-46-9P	168542-47-0P
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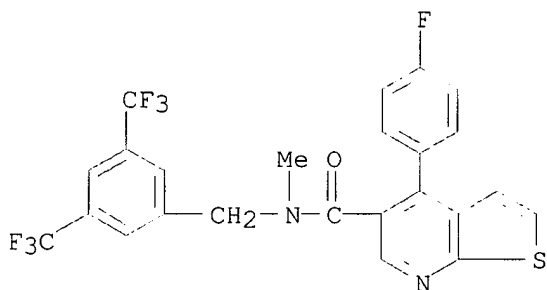
168543-14-4P 168543-15-5P 168543-16-6P 168543-17-7P 168543-18-8P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and
 related compds. as tachykinin antagonists and inhibitors of plasma
 extravasation)

IT 168541-24-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and
 related compds. as tachykinin antagonists and inhibitors of plasma
 extravasation)

RN 168541-24-0 HCAPLUS

CN Thieno[2,3-b]pyridine-5-carboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]me
 thyl]-4-(4-fluorophenyl)-N-methyl- (9CI) (CA INDEX NAME)



L118 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1995:257714 HCAPLUS

DN 122:56051

TI Condensed heterocyclic compounds, their production and use

IN Natsugari, Hideaki; Ikeda, Hitoshi; Ishimaru, Takenori; Doi, Takayuki

PA Takeda Chemical Industries, Ltd., Japan

SO Eur. Pat. Appl., 161 pp.

CODEN: EPXXDW

DT Patent

LA English

IC ICM C07D217-24

ICS C07D217-26; C07D311-18; C07D215-54; C07D471-04; C07D311-76;

C07D215-22; A61K031-47; A61K031-37

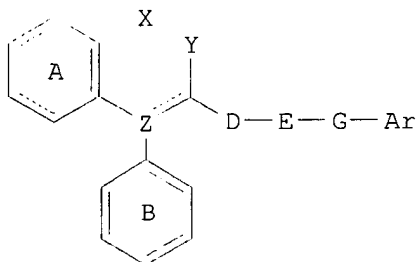
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 585913	A2	19940309	EP 1993-114024	19930902 <--
	EP 585913	A3	19940525		
	EP 585913	B1	19971229		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	NO 9303133	A	19940307	NO 1993-3133	19930902 <--
	NO 179904	B	19960930		
	NO 179904	C	19970108		
	US 5482967	A	19960109	US 1993-114841	19930902 <--
	AT 161530	E	19980115	AT 1993-114024	19930902 <--
	CA 2105518	AA	19940305	CA 1993-2105518	19930903 <--
	AU 9346132	A1	19940310	AU 1993-46132	19930903 <--
	AU 667739	B2	19960404		
	FI 9303857	A	19940517	FI 1993-3857	19930903 <--
	JP 07010844	A2	19950113	JP 1993-220333	19930903 <--

	HU 67284	A2	19950328	HU 1993-2499	19930903 <--
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PRAI	JP 1992-237481		19920904	<--	
	JP 1993-103328		19930428	<--	
	US 1993-114841		19930902	<--	
OS	MARPAT 122:56051				
GI					



I

- AB Novel compds. represented by I were prepd.; ring A may be substituted; ring B represents an optionally substituted benzene ring; either X or Y represents -NR₁- (R₁ represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group or an optionally substituted amino group), -O- or -S-, the other representing -CO-, -CS-, or -C(R₂)R_{2a}- (R₂ and R_{2a} independently represent a hydrogen atom or an optionally substituted hydrocarbon group), or either X or Y represents -N=, the other representing =CR₃- (R₃ represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted amino group, a substituted hydroxyl group or a mercapto group substituted by an optionally substituted hydrocarbon group); ---- represents a single or double bond; when ---- is a single bond, Z represents -CR₄- (R₄ represents a hydrogen atom, hydroxyl group or an optionally substituted hydrocarbon group) or a nitrogen atom, or (ii) when ---- is a double bond, Z represents a carbon atom. D represents a C1-3 alkylene group which may be substituted by an oxo group or a thioxo group, or D and Y, taken together, may form a 5- to 7-membered ring which may be substituted by an oxo group or a thioxo group; E represents -NR₅- (R₅ represents a hydrogen atom or an optionally substituted hydrocarbon group), -O- or -S-(O)_n- (n is 0, 1 or 2), or R₅ and Y, taken together, may form a 5- to 7-membered ring which may be substituted by an oxo group or a thioxo group. G represents a bond or a C1-3 alkylene group. Ar represents an optionally substituted aryl or heterocyclic group. Some representative prepd. compds. were benzopyran-, quinoline-, isoquinoline- and quinoxalinecarboxamides. I and its salts have an excellent activity of inhibiting ACAT, lowering cholesterol in blood and inhibiting tachykinin receptor (test data given).
- ST heterocyclic compd prepn biol activity; cholesterol acyl transferase inhibitor heterocyclic compd; blood cholesterol lowering heterocyclic compd; tachykinin receptor inhibiting heterocyclic compd; benzopyran compd prepn biol activity; isoquinoline compd prepn biol activity; quinoline compd prepn biol activity; quinoxaline compd prepn biol activity
- IT Anticholesteremics and Hypolipemics
(condensed heterocyclic compds.)
- IT **Kinin receptors**
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tachykinin**, inhibitors for, condensed heterocyclic compds.)

as)
IT 9027-63-8, Cholesterol acyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(condensed heterocyclic compds. as inhibitors for)

IT 159816-08-7P 159816-09-8P 159816-10-1P 159816-11-2P 159816-12-3P
159816-13-4P 159816-14-5P 159816-15-6P 159816-16-7P 159816-17-8P
159816-18-9P 159816-19-0P 159816-20-3P 159816-21-4P 159816-22-5P
159816-23-6P 159816-24-7P 159816-25-8P 159816-26-9P 159816-27-0P
159816-28-1P 159816-29-2P 159816-30-5P 159816-31-6P 159816-32-7P
159816-33-8P 159816-34-9P 159816-35-0P 159816-36-1P 159816-37-2P
159816-38-3P 159816-39-4P 159816-40-7P 159816-41-8P 159816-42-9P
159816-43-0P 159816-44-1P 159816-45-2P 159816-46-3P 159816-47-4P
159816-48-5P 159816-49-6P 159816-50-9P 159816-51-0P 159816-52-1P
159816-53-2P 159816-54-3P 159816-55-4P 159816-56-5P 159816-57-6P
159816-58-7P 159816-59-8P 159816-60-1P 159816-61-2P 159816-62-3P
159816-63-4P 159816-64-5P 159816-65-6P 159816-66-7P 159816-67-8P
159816-68-9P 159816-69-0P 159816-70-3P 159816-71-4P 159816-72-5P
159816-73-6P 159816-74-7P 159816-75-8P 159816-76-9P 159816-77-0P
159816-78-1P 159816-79-2P 159816-80-5P 159816-81-6P 159816-82-7P
159816-83-8P 159816-84-9P 159816-85-0P 159816-86-1P 159816-87-2P
159816-88-3P 159816-89-4P 159816-90-7P 159816-91-8P 159816-92-9P
159816-93-0P 159816-94-1P 159816-95-2P 159816-96-3P 159816-97-4P
159816-98-5P 159816-99-6P 159817-00-2P 159817-01-3P 159817-02-4P
159817-03-5P 159817-04-6P 159817-05-7P 159817-06-8P 159817-07-9P
159817-08-0P 159817-09-1P 159817-10-4P 159817-11-5P 159817-12-6P
159817-13-7P 159817-14-8P 159817-15-9P 159817-16-0P 159817-17-1P
159817-18-2P 159817-19-3P 159817-20-6P 159817-21-7P 159817-22-8P
159817-23-9P 159817-24-0P 159817-25-1P 159817-26-2P 159817-27-3P
159817-28-4P 159817-29-5P 159817-30-8P 159817-31-9P 159817-32-0P
159817-33-1P 159817-34-2P 159817-35-3P 159817-36-4P 159817-37-5P
159817-38-6P 159817-39-7P 159817-40-0P 159817-41-1P 159817-42-2P
159817-43-3P 159817-44-4P 159817-45-5P 159817-46-6P 159817-47-7P
159817-48-8P 159817-49-9P 159817-50-2P 159817-51-3P 159817-52-4P
159817-53-5P 159817-54-6P 159817-55-7P 159817-56-8P 159817-57-9P
159817-58-0P 159817-59-1P 159817-60-4P 159817-61-5P 159817-62-6P
159817-63-7P 159817-64-8P 159817-65-9P 159817-66-0P 159817-67-1P
159817-68-2P 159817-69-3P 159817-70-6P 159817-71-7P 159817-72-8P
159817-73-9P 159817-74-0P 159817-75-1P 159817-76-2P 159817-77-3P
159817-78-4P 159817-79-5P 159817-80-8P 159817-81-9P 159817-82-0P
159817-83-1P 159817-84-2P 159817-85-3P 159817-86-4P 159817-87-5P
159817-88-6P 159817-89-7P 159817-90-0P 159817-91-1P 159817-92-2P
159817-93-3P 159817-94-4P 159817-95-5P 159817-96-6P 159817-97-7P
159817-98-8P 159817-99-9P 159818-00-5P 159818-01-6P 159818-02-7P
159818-03-8P 159818-04-9P 159818-05-0P 159818-06-1P 159818-07-2P
159818-08-3P 159818-09-4P 159818-10-7P 159818-11-8P 159818-12-9P
159818-13-0P 159818-14-1P 159818-15-2P 159818-16-3P 159818-17-4P
159818-18-5P 159818-19-6P 159818-20-9P 159818-21-0P 159818-22-1P
159818-23-2P 159818-24-3P 159818-25-4P 159818-26-5P 159818-27-6P
159818-28-7P 159818-29-8P 159818-30-1P 159818-31-2P 159818-32-3P
159818-33-4P 159818-34-5P 159818-35-6P 159818-36-7P 159818-37-8P
159818-38-9P 159818-39-0P 159818-40-3P 159818-41-4P 159818-42-5P
159818-43-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activity of)

IT 159818-44-7P 159818-45-8P 159818-46-9P 159818-47-0P 159818-48-1P
159818-49-2P 159818-50-5P 159818-51-6P 159818-52-7P 159818-53-8P
159818-54-9P 159818-55-0P 159818-56-1P 159818-57-2P 159818-58-3P
159818-59-4P 159818-60-7P 159818-61-8P 159818-62-9P
159818-63-0P 159818-64-1P **159818-65-2P 159818-66-3P**
159818-67-4P 159818-68-5P 159818-69-6P
159818-70-9P 159818-71-0P 159818-72-1P

159818-73-2P 159818-74-3P 159818-75-4P 159818-76-5P
 159818-77-6P 159818-78-7P 159818-79-8P 159818-80-1P 159818-81-2P
 159818-82-3P 159818-83-4P 159818-84-5P 159818-85-6P 159818-86-7P
 159818-87-8P 159818-88-9P 159818-89-0P 159818-90-3P 159818-91-4P
 159818-92-5P 159818-93-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. and biol. activity of)

IT	32893-29-1P	52980-94-6P	125064-54-2P	137711-58-1P	137711-72-9P
	142256-48-2P	152818-34-3P	152818-35-4P	152818-37-6P	152818-38-7P
	152818-40-1P	152818-43-4P	152818-47-8P	152818-48-9P	152818-49-0P
	152818-50-3P	152818-51-4P	152818-52-5P	152818-53-6P	152818-54-7P
	152818-55-8P	159818-94-7P	159818-95-8P	159818-96-9P	159818-97-0P
	159818-98-1P	159818-99-2P	159819-00-8P	159819-01-9P	159819-02-0P
	159819-03-1P	159819-04-2P	159819-05-3P	159819-06-4P	159819-07-5P
	159819-08-6P	159819-09-7P	159819-10-0P	159819-11-1P	159819-12-2P
	159819-13-3P	159819-14-4P	159819-15-5P	159819-16-6P	159819-17-7P
	159819-18-8P	159819-19-9P	159819-20-2P	159819-21-3P	159819-22-4P
	159819-23-5P	159819-24-6P	159819-25-7P	159819-26-8P	159819-27-9P
	159819-28-0P	159819-29-1P	159819-30-4P	159819-31-5P	159819-32-6P
	159819-33-7P	159819-34-8P	159819-35-9P	159819-36-0P	159819-37-1P
	159819-38-2P	159819-39-3P	159819-40-6P	159819-41-7P	159819-42-8P
	159819-43-9P	159819-44-0P	159819-45-1P	159819-46-2P	159819-47-3P
	159819-48-4P	159819-49-5P	159819-50-8P	159819-51-9P	159819-52-0P
	159819-53-1P	159819-54-2P	159819-55-3P	159819-56-4P	159819-57-5P
	159819-58-6P	159819-59-7P	159819-60-0P	159819-61-1P	159819-62-2P
	159819-63-3P	159819-64-4P	159819-65-5P	159819-66-6P	159819-67-7P
	159819-68-8P	159819-69-9P	159819-70-2P	159819-71-3P	159819-72-4P
	159819-73-5P	159819-74-6P	159819-75-7P	159819-76-8P	159819-77-9P
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	159819-83-7P	159819-84-8P	159819-85-9P	159819-86-0P	159819-87-1P
	159819-88-2P	159819-89-3P	159819-90-6P	159819-91-7P	159819-92-8P
	159819-93-9P	159819-94-0P	159819-95-1P	159819-96-2P	159819-97-3P
	159819-98-4P	159819-99-5P	159820-00-5P	159820-01-6P	159820-02-7P
	159820-03-8P	159820-04-9P	159820-05-0P	159820-06-1P	159820-07-2P
	159820-08-3P	159820-09-4P	159820-10-7P	159820-11-8P	159820-12-9P
	159820-13-0P	159820-14-1P	159820-15-2P	159820-16-3P	159820-17-4P
	159820-18-5P	159820-19-6P	159820-20-9P	159820-21-0P	159820-22-1P
	159820-25-4P	159820-26-5P	159820-30-1P	159820-34-5P	159820-35-6P
	159820-36-7P	159820-38-9P			

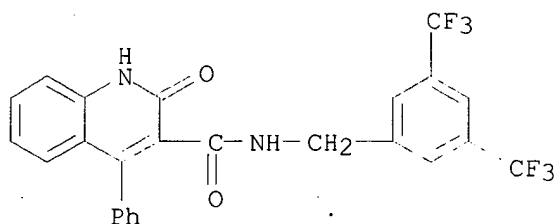
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. and reaction of, in prepn. of biol. active condensed heterocyclic compds.)

IT	50-00-0, Formaldehyde, reactions	75-30-9, Isopropyl iodide	79-04-9, Chloroacetyl chloride	100-39-0, Benzyl bromide	100-46-9, Benzylamine, reactions	105-53-3, Diethyl malonate	107-15-3, 1,2-Ethanediamine, reactions	108-00-9, 124-63-0, Methanesulfonyl chloride	135-02-4, o-Anisaldehyde	367-25-9, 2,4-Difluoroaniline	447-61-0, 623-12-1, 4-Chloroanisole	685-87-0, Diethyl bromomalonate	933-88-0, o-Toluoyl chloride	1470-57-1, 2426-02-0, 5266-85-3, 5292-43-3, tert-Butyl bromoacetate	5779-95-3, 3,5-Dimethylbenzaldehyde	5959-36-4, 6850-57-3, 2-Methoxybenzylamine	7035-02-1, 2-Methoxybenzyl chloride	7417-18-7, 7649-92-5, 18936-32-8, 24544-04-5, 2,6-Diisopropylaniline	25808-30-4, 26832-76-8, 28773-68-4, 32247-96-4, 33184-58-6, 37393-68-3, 37617-98-4, 52605-49-9, 68817-71-0, 78945-92-3, 78945-97-8, 81698-18-2, 85068-29-7, 92795-47-6, 128831-20-9, 128832-35-9, 135030-74-9, 136280-97-2, 136281-10-2, 137711-59-2, 137711-72-9, 137711-73-0, 142256-41-5, 142256-46-0, 142256-53-9, 152818-36-5, 159820-23-2, 159820-24-3, 159820-27-6, 159820-28-7, 159820-29-8, 159820-31-2, 159820-32-3, 159820-33-4, 159820-37-8
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RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, in prepn. of biol. active condensed heterocyclic compds.)
 IT **159818-59-4P**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (prepn. and biol. activity of)
 RN 159818-59-4 HCAPLUS
 CN 3-Quinolinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-1,2-dihydro-2-oxo-4-phenyl- (9CI) (CA INDEX NAME)



=> d his

(FILE 'HOME' ENTERED AT 07:01:07 ON 04 MAR 2003)
 SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003

L1 STR
 L2 19 S L1
 L3 594 S L1 FUL
 SAV L3 KWON071/A

FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003

L4 40 S L3
 E BUSER S/AU
 L5 10 S E3,E6,E7
 E FORD A/AU
 L6 33 S E3,E16,E17
 L7 37 S E63,E65
 E FORD TONY/AU
 E HOFFMANN T/AU
 L8 135 S E3-E9
 E HOFFMANN TOR/AU
 L9 57 S E4
 E LENZ B/AU
 L10 29 S E3-E9
 E SLEIGHT A/AU
 L11 52 S E4,E6-E8
 E VANKAN P/AU
 L12 23 S E3-E5
 E ROCHE/PA,CS
 L13 21472 S E3,E4
 L14 61 S E27-E46
 E ROHAN/PA,CS
 L15 2 S E3,E4
 L16 10 S L4 AND L5-L15
 E PROSTATE/CT
 E E5+ALL
 L17 2309 S E2
 L18 1988 S E12
 L19 22609 S E20-E19+NT

L20 1 S L4 AND L17-L19
 L21 1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
 L22 1 S L20,L21
 L23 1 S L22 AND L16
 L24 969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
 L25 5 S L24 AND L17-L19
 L26 2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
 L27 6 S L25,L26
 L28 1 S L23 AND L27
 L29 5 S L27 NOT L28
 SEL DN AN 1 4 5
 L30 3 S E1-E7 AND L29
 L31 4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
 L32 4 S L28,L30,L31
 L33 39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
 L34 47 S GR205171 OR GR()(205171 OR 205 171)
 L35 5 S HSP117 OR HSP 117
 L36 36 S L703606 OR L()(703606 OR 703 606)
 L37 23 S L668169 OR L()(668169 OR 668 169)
 L38 4 S LY303241 OR LY()(303241 OR 303 241)
 L39 12 S LY306740 OR LY()(306740 OR 306 740)
 L40 21 S MK869 OR MK 869
 L41 6 S R544 OR R 544
 L42 5 S SPANTIDE III
 L43 11 S WIN62577 OR WIN()(62577 OR 62 577)
 L44 5 S GR103537 OR GR()(103537 OR 103 537)
 L45 13 S L758298 OR L()(758298 OR 758 298)
 L46 9 S NKP608 OR NKP 608
 L47 17 S CGP49823 OR CGP()(49823 OR 49 823)
 L48 494 S CP96345 OR CP()(96345 OR 96 345)
 L49 246 S CP99994 OR CP()(99994 OR 99 994)
 L50 24 S CP122721 OR CP()(122721 OR 122 721)
 L51 129 S FK888 OR FK 888
 L52 119 S GR82334 OR GR()(82334 OR 82 334)
 L53 41 S GR94800 OR GR()(94800 OR 94 800)
 L54 20 S L733060 OR L()(733060 OR 733 060)
 L55 16 S L742694 OR L()(742694 OR 742 694)
 L56 10 S L754030 OR L()(754030 OR 754 030)
 L57 30 S LY303870 OR LY()(303870 OR 303 870)
 L58 9 S MEN11149 OR MEN()(11149 OR 11 149)
 L59 10 S PD154075 OR PD()(154075 OR 154 075)
 L60 250 S RP67580 OR RP()(67580 OR 67 580)
 L61 18 S RPR100893 OR RPR()(100893 OR 100 893)
 L62 1 S SPENDIDE
 L63 32 S SENDIDE
 L64 55 S SPANTIDE II
 L65 217 S SR140333 OR SR()(140333 OR 140 333)
 L66 0 S WIN41708 OR WIN()(41708 OR 41 708)
 L67 11 S WIN62577 OR WIN()(62577 OR 62 577)
 L68 410 S SR48968 OR SR()(48968 OR 48 968)
 L69 69 S L659877 OR L()(659877 OR 659 877)
 L70 74 S MEN10627 OR MEN()(10627 OR 10 627)
 L71 14 S SR144190 OR SR()(144190 OR 144 190)
 L72 41 S GR94800 OR GR()(94800 OR 94 800)
 L73 149 S SR142801 OR SR()(142801 OR 142 801)
 L74 159 S R820 OR R 820
 L75 14 S R486 OR R 486
 L76 13 S SB222200 OR SB()(222200 OR 222 200)
 L77 13 S L758298 OR L()(758298 OR 758 298)
 L78 0 S NK608 OR NK 608
 L79 3 S MK608 OR MK 608
 L80 2 S CGP47899 OR CGP()(47899 OR 47 899)
 L81 16 S MEN11467 OR MEN()(11467 OR 11 467)

L82 18 S GR203040 OR GR() (203040 OR 203 040)
 L83 13 S L732138 OR L() (732138 OR 732 138)
 L84 1 S L4 AND L34-L83
 L85 2 S WIN41908 OR WIN() (41908 OR 41 908)
 L86 349 S SPANTIDE
 L87 1 S L4 AND L85,L86
 L88 1 S L84,L87
 SEL RN

FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003

L89 186 S E8-E193
 L90 129 S L89 AND L3
 L91 1 S 351383-26-1
 L92 56 S L89 NOT L90,L91
 L93 7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
 L94 6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
 L95 43 S L92 NOT L93,L94
 L96 6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1

FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003

L97 46 S L95,L96

FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003

L98 964 S L97
 L99 3 S L4 AND L98
 L100 3 S L88,L99
 L101 3 S L100 AND L4-L16
 L102 6 S L32,L101
 E TACKYKININ RECEPTOR/CT
 E TACHYKININ RECEPTOR/CT
 L103 1581 S E5,E6
 L104 223 S E14
 E E4+ALL
 L105 3707 S E10,E11,E9+NT
 E E27+ALL
 L106 2037 S E8,E7+NT
 E E6+ALL
 L107 3401 S E7,E8,E6+NT
 E E20
 L108 2087 S E3-E21
 L109 638 S E22-E25
 L110 13 S L4 AND L103-L109
 L111 3 S L102 AND L110
 L112 6 S L102,L111
 L113 6 S L112 AND L4-L88
 L114 3 S L113 AND L17-L19
 L115 2 S L113 AND (BHP OR BENIGN(L) PROSTAT?(L) HYPER?)
 L116 4 S L114,L115
 L117 12 S L110,L113 NOT L116
 L118 12 S L117 AND L4-L88,L98-L109

FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

FILE 'HCAPLUS' ENTERED AT 08:04:40 ON 04 MAR 2003

FILE 'EMBASE' ENTERED AT 08:05:33 ON 04 MAR 2003

E BENIGN PROSTAT/CT
 E E4+ALL
 E E2+ALL
 L119 9419 S E1
 L120 6565 S E7/BI OR E8/BI OR E11-E21/BI
 L121 6986 S BHP OR BENIGN(L) PROSTAT?(L) HYPER?
 L122 0 S L3

L123 1337 S L24
 E NERUOKININE 1 RECEPTOR ANTAGONIST/CT
 E NEUROKININE 1 RECEPTOR ANTAGONIST/CT
 E NEUROKININ 1 RECEPTOR ANTAGONIST/CT
 E E3+ALL
 L124 663 S E1+NT
 L125 1 S L119-L121 AND L123,L124

FILE 'MEDLINE' ENTERED AT 08:08:33 ON 04 MAR 2003

L126 0 S L3
 L127 13566 S L120 OR L121
 E BENIGN PROSTAT/CT
 E E5+ALL
 E E2+ALL
 L128 11113 S E5+NT
 L129 1074 S E17/BI OR E23/BI
 L130 13795 S L127-L129
 L131 1451 S L24
 E NEUROKININ 1 RECEPTOR/CT
 E E4+ALL
 E E2+ALL
 L132 2169 S E15+NT
 L133 2169 S E15/CN
 L134 3283 S E14+NT
 L135 680 S E14/CN
 L136 0 S L130 AND L131-L135

=> fil embase

FILE 'EMBASE' ENTERED AT 08:10:58 ON 04 MAR 2003

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FILE COVERS 1974 TO 27 Feb 2003 (20030227/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l125

L125 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
 AN 97132738 EMBASE
 DN 1997132738
 TI The 98th Annual Meeting of the American Society for Clinical Pharmacology
 and Therapeutics.
 AU Heydorn W.E.
 CS W.E. Heydorn, Pharmaceutical Operations, Synaptic Pharmaceutical
 Corporation, 215 College Road, Paramus, NJ 07652, United States.
 heydorn@aol.com
 SO Expert Opinion on Investigational Drugs, (1997) 6/4 (453-457).
 Refs: 10
 ISSN: 1354-3784 CODEN: EOIDER
 CY United Kingdom
 DT Journal; Conference Article
 FS 008 Neurology and Neurosurgery
 015 Chest Diseases, Thoracic Surgery and Tuberculosis
 022 Human Genetics
 028 Urology and Nephrology
 049 Forensic Science Abstracts
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions TitlesDrug Literature Index
 LA English

SL English

AB The 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics was held on March 5-8, 1997. Over 850 researchers and clinicians pre-registered for this meeting. Papers presented at the conference focused on new observations. Firstly, novel therapeutic agents were discussed, then compounds that represent standard therapy for a number of different disease states were addressed. State of the art lectures provided concise updates on the status of a number of different issues. The following is a summary of some of the highlights and presentations at the conference. This summary is divided into four sections. Section 1 focuses on the Public Policy Debate on the ethics and utility of the placebo-controlled trial. Part 2 is a summary of the current status of gene therapy with particular reference to cystic fibrosis treatment. Part 3 is a summary of data on two recently approved compounds (donepezil and zafirlukast). The last part of this article discusses the results of drug therapy in two different disease states (**benign prostatic hypertrophy** and migraine).

CT Medical Descriptors:

*cystic fibrosis

*gene therapy

*medical ethics

*migraine

*prostate hypertrophy

alzheimer disease: DT, drug therapy

asthma: DT, drug therapy

clinical pharmacology

clinical trial

conference paper

drug approval

drug metabolism

human

hypotension: SI, side effect

medical research

vertigo: SI, side effect

Drug Descriptors:

cholinesterase inhibitor: PD, pharmacology

cholinesterase inhibitor: PK, pharmacokinetics

cholinesterase inhibitor: DT, drug therapy

cholinesterase inhibitor: CT, clinical trial

donepezil: PD, pharmacology

donepezil: PK, pharmacokinetics

donepezil: DT, drug therapy

donepezil: CT, clinical trial

doxazosin: PK, pharmacokinetics

doxazosin: CT, clinical trial

doxazosin: DT, drug therapy

eletriptan: DT, drug therapy

eletriptan: PD, pharmacology

eletriptan: CT, clinical trial

eletriptan: PK, pharmacokinetics

lanepitant: CT, clinical trial

lanepitant: DT, drug therapy

lanepitant: PD, pharmacology

leukotriene receptor blocking agent: PD, pharmacology

leukotriene receptor blocking agent: PK, pharmacokinetics

leukotriene receptor blocking agent: DT, drug therapy

leukotriene receptor blocking agent: IT, drug interaction

leukotriene receptor blocking agent: CT, clinical trial

ly 303780

neurokinin 1 receptor antagonist: PD, pharmacology

neurokinin 1 receptor antagonist: DT, drug therapy

neurokinin 1 receptor antagonist: CT, clinical trial

placebo

serotonin 1d receptor agonist: CT, clinical trial
 serotonin 1d receptor agonist: DT, drug therapy
 serotonin 1d receptor agonist: PK, pharmacokinetics
 serotonin 1d receptor agonist: PD, pharmacology
 tacrine: DT, drug therapy
 terazosin: AE, adverse drug reaction
 terazosin: DT, drug therapy
 warfarin: IT, drug interaction
 warfarin: PK, pharmacokinetics
 zafirlukast: PD, pharmacology
 zafirlukast: PK, pharmacokinetics
 zafirlukast: IT, drug interaction
 zafirlukast: CT, clinical trial
 zafirlukast: DT, drug therapy
 unclassified drug
 RN (donepezil) 120011-70-3, 120014-06-4; (doxazosin) 74191-85-8; (eletriptan)
 143322-58-1; (lanepitant) 167678-33-3, 170508-05-1, 170566-84-4; (tacrine)
 1684-40-8, 3198-41-2, 321-64-2; (terazosin) 63074-08-8, 63590-64-7;
 (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2;
 (zafirlukast) 107753-78-6
 CN (1) Ly 303780
 CO (1) Lilly

=> d his

(FILE 'HOME' ENTERED AT 07:01:07 ON 04 MAR 2003)
 SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003

L1 STR
 L2 19 S L1
 L3 594 S L1 FUL
 SAV L3 KWON071/A

FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003

L4 40 S L3
 E BUSER S/AU
 L5 10 S E3,E6,E7
 E FORD A/AU
 L6 33 S E3,E16,E17
 L7 37 S E63,E65
 E FORD TONY/AU
 E HOFFMANN T/AU
 L8 135 S E3-E9
 E HOFFMANN TOR/AU
 L9 57 S E4
 E LENZ B/AU
 L10 29 S E3-E9
 E SLEIGHT A/AU
 L11 52 S E4,E6-E8
 E VANKAN P/AU
 L12 23 S E3-E5
 E ROCHE/PA,CS
 L13 21472 S E3,E4
 L14 61 S E27-E46
 E ROHAN/PA,CS
 L15 2 S E3,E4
 L16 10 S L4 AND L5-L15
 E PROSTATE/CT
 E E5+ALL
 L17 2309 S E2
 L18 1988 S E12

L19 22609 S E20-E19+NT
L20 1 S L4 AND L17-L19
L21 1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L22 1 S L20,L21
L23 1 S L22 AND L16
L24 969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
L25 5 S L24 AND L17-L19
L26 2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L27 6 S L25,L26
L28 1 S L23 AND L27
L29 5 S L27 NOT L28
SEL DN AN 1 4 5
L30 3 S E1-E7 AND L29
L31 4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
L32 4 S L28,L30,L31
L33 39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
L34 47 S GR205171 OR GR()(205171 OR 205 171)
L35 5 S HSP117 OR HSP 117
L36 36 S L703606 OR L()(703606 OR 703 606)
L37 23 S L668169 OR L()(668169 OR 668 169)
L38 4 S LY303241 OR LY()(303241 OR 303 241)
L39 12 S LY306740 OR LY()(306740 OR 306 740)
L40 21 S MK869 OR MK 869
L41 6 S R544 OR R 544
L42 5 S SPANTIDE III
L43 11 S WIN62577 OR WIN()(62577 OR 62 577)
L44 5 S GR103537 OR GR()(103537 OR 103 537)
L45 13 S L758298 OR L()(758298 OR 758 298)
L46 9 S NKP608 OR NKP 608
L47 17 S CGP49823 OR CGP()(49823 OR 49 823)
L48 494 S CP96345 OR CP()(96345 OR 96 345)
L49 246 S CP99994 OR CP()(99994 OR 99 994)
L50 24 S CP122721 OR CP()(122721 OR 122 721)
L51 129 S FK888 OR FK 888
L52 119 S GR82334 OR GR()(82334 OR 82 334)
L53 41 S GR94800 OR GR()(94800 OR 94 800)
L54 20 S L733060 OR L()(733060 OR 733 060)
L55 16 S L742694 OR L()(742694 OR 742 694)
L56 10 S L754030 OR L()(754030 OR 754 030)
L57 30 S LY303870 OR LY()(303870 OR 303 870)
L58 9 S MEN11149 OR MEN()(11149 OR 11 149)
L59 10 S PD154075 OR PD()(154075 OR 154 075)
L60 250 S RP67580 OR RP()(67580 OR 67 580)
L61 18 S RPR100893 OR RPR()(100893 OR 100 893)
L62 1 S SPENDIDE
L63 32 S SENDIDE
L64 55 S SPANTIDE II
L65 217 S SR140333 OR SR()(140333 OR 140 333)
L66 0 S WIN41708 OR WIN()(41708 OR 41 708)
L67 11 S WIN62577 OR WIN()(62577 OR 62 577)
L68 410 S SR48968 OR SR()(48968 OR 48 968)
L69 69 S L659877 OR L()(659877 OR 659 877)
L70 74 S MEN10627 OR MEN()(10627 OR 10 627)
L71 14 S SR144190 OR SR()(144190 OR 144 190)
L72 41 S GR94800 OR GR()(94800 OR 94 800)
L73 149 S SR142801 OR SR()(142801 OR 142 801)
L74 159 S R820 OR R 820
L75 14 S R486 OR R 486
L76 13 S SB222200 OR SB()(222200 OR 222 200)
L77 13 S L758298 OR L()(758298 OR 758 298)
L78 0 S NK608 OR NK 608
L79 3 S MK608 OR MK 608
L80 2 S CGP47899 OR CGP()(47899 OR 47 899)

L81 16 S MEN11467 OR MEN() (11467 OR 11 467)
 L82 18 S GR203040 OR GR() (203040 OR 203 040)
 L83 13 S L732138 OR L() (732138 OR 732 138)
 L84 1 S L4 AND L34-L83
 L85 2 S WIN41908 OR WIN() (41908 OR 41 908)
 L86 349 S SPANTIDE
 L87 1 S L4 AND L85,L86
 L88 1 S L84,L87
 SEL RN

FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003

L89 186 S E8-E193
 L90 129 S L89 AND L3
 L91 1 S 351383-26-1
 L92 56 S L89 NOT L90,L91
 L93 7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
 L94 6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
 L95 43 S L92 NOT L93,L94
 L96 6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1

FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003

L97 46 S L95,L96

FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003

L98 964 S L97
 L99 3 S L4 AND L98
 L100 3 S L88,L99
 L101 3 S L100 AND L4-L16
 L102 6 S L32,L101
 E TACKYKININ RECEPTOR/CT
 E TACHYKININ RECEPTOR/CT
 L103 1581 S E5,E6
 L104 223 S E14
 E E4+ALL
 L105 3707 S E10,E11,E9+NT
 E E27+ALL
 L106 2037 S E8,E7+NT
 E E6+ALL
 L107 3401 S E7,E8,E6+NT
 E E20
 L108 2087 S E3-E21
 L109 638 S E22-E25
 L110 13 S L4 AND L103-L109
 L111 3 S L102 AND L110
 L112 6 S L102,L111
 L113 6 S L112 AND L4-L88
 L114 3 S L113 AND L17-L19
 L115 2 S L113 AND (BHP OR BENIGN(L) PROSTAT?(L) HYPER?)
 L116 4 S L114,L115
 L117 12 S L110,L113 NOT L116
 L118 12 S L117 AND L4-L88,L98-L109

FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

FILE 'HCAPLUS' ENTERED AT 08:04:40 ON 04 MAR 2003

FILE 'EMBASE' ENTERED AT 08:05:33 ON 04 MAR 2003

E BENIGN PROSTAT/CT
 E E4+ALL
 E E2+ALL
 L119 9419 S E1
 L120 6565 S E7/BI OR E8/BI OR E11-E21/BI
 L121 6986 S BHP OR BENIGN(L) PROSTAT?(L) HYPER?

L122 0 S L3
L123 1337 S L24
E NERUOKININE 1 RECEPTOR ANTAGONIST/CT
E NEUROKININE 1 RECEPTOR ANTAGONIST/CT
E NEUROKININ 1 RECEPTOR ANTAGONIST/CT
E E3+ALL
L124 663 S E1+NT
L125 1 S L119-L121 AND L123,L124

FILE 'MEDLINE' ENTERED AT 08:08:33 ON 04 MAR 2003

L126 0 S L3
L127 13566 S L120 OR L121
E BENIGN PROSTAT/CT
E E5+ALL
E E2+ALL
L128 11113 S E5+NT
L129 1074 S E17/BI OR E23/BI
L130 13795 S L127-L129
L131 1451 S L24
E NEUROKININ 1 RECEPTOR/CT
E E4+ALL
E E2+ALL
L132 2169 S E15+NT
L133 2169 S E15/CN
L134 3283 S E14+NT
L135 680 S E14/CN
L136 0 S L130 AND L131-L135

FILE 'EMBASE' ENTERED AT 08:10:58 ON 04 MAR 2003

FILE 'WPIX' ENTERED AT 08:11:12 ON 04 MAR 2003

L137 2559 S L120/BIX OR L121/BIX OR L129/BIX
L138 168 S L24/BIX
L139 246 S (TACHYKININ(L)RECEPTOR)/BIX
L140 13 S L137 AND L138,L139
L141 6 S L140 AND F431/M0,M1,M2,M3,M4,M5,M6
L142 17637 S (B07-D04 OR B07-D04B OR B07-D04C OR C07-D04 OR C07-D04B OR C0
L143 13892 S (B06-H OR C06-H)/MC
L144 4 S L140 AND L142,L143
L145 6 S L141,L144
SEL DN AN 1 6
L146 2 S E1-E4 AND L145

FILE 'HCAPLUS' ENTERED AT 08:19:31 ON 04 MAR 2003

SEL PN APPS L16

FILE 'WPIX' ENTERED AT 08:19:54 ON 04 MAR 2003

L147 10 S E5-E97
L148 1 S L147 AND L137
L149 1 S L147 AND A61P013/IC, ICM, ICS, ICA, ICI
L150 0 S L148,L149 NOT L146